IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER HEALTHCARE AG, ALCON, INC. and ALCON RESEARCH, LTD., Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	)	Civil Action No. 06-234-SLR

PLAINTIFFS' POST-TRIAL BRIEF ON VALIDITY

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Teva's post-trial invalidity brief avoids the trial record and ignores or misstates the governing law. The record fails to support any of Teva's myriad invalidity theories. Unfazed, Teva argues that the Court should disregard much of the record, mischaracterizes other portions, and even relies on evidence not in the trial record at all. Teva compounds its factual deficiencies with flawed legal arguments that serially violate one established legal tenet after another.

Teva's primary invalidity challenge, its assertion that claim 1 of the '830 patent is obvious, is premised on a fundamental error. The problem that the '830 patent addresses is that the existing products in 1998 were deficient in treating and preventing serious ocular infections, and a new topical ophthalmic antibiotic composition was needed to overcome that problem. The critical issue in addressing this problem was the selection of the active ingredient to be used in the composition – that is the '830 patent's invention. The evidence established that the person of ordinary skill ("POOS") addressing this issue would have skills and experience in microbiology and/or ophthalmology (as did the inventors and skilled workers in the field). From the perspective of this POOS, moxifloxacin would have been far from an obvious choice; rather, the art taught away from using it, as it would have been viewed as a particularly poor choice to solve the problem identified in the patent and the field. That the claimed invention has turned out to be a breakthrough that has transformed the field of treating and preventing ophthalmic infections was completely unexpected and ran contrary to the conventional wisdom.

Teva wholly ignores whether it would have been obvious to select moxifloxacin for use in a topical ophthalmic composition. It assumes that moxifloxacin had already been selected for use in an ophthalmic composition. As a result, Teva defines the POOS as a pharmaceutical scientist who formulates compositions and lacks expertise in microbiology and ophthalmology – a person who even Teva's expert admits does not have the expertise to determine what active

ingredient should be selected. Teva focuses on whether this POOS, having been instructed to use moxifloxacin in an ophthalmic composition, could prepare the claimed ophthalmic composition – which completely sidesteps the relevant inquiry. Teva compounds its error by violating numerous basic principles of obviousness law: failing to consider the prior art as a whole, arguing interpretations of the prior art through the eyes of its attorneys rather than the POOS, and relying on the inventors' own work to try to show that their invention was obvious.

Teva's other invalidity arguments fare no better. Teva's contention that the '942 patent anticipates the '830 patent is unsupported by the text of the '942 patent and contravenes controlling authority. Indeed, Teva apparently recognizes as much and thus, revealingly, relies in its anticipation argument on references other than the '942 patent and interpretations of the '942 patent that not even its own expert, who in any event lacks the skills of a POOS, advanced.

With regard to Teva's best mode argument, there was no dispute regarding the inventors' subjective best mode of practicing the invention – a solution of moxifloxacin – and similarly no dispute that this was disclosed. Teva therefore mischaracterizes the record to contend that Dr. Stroman had a preference for a composition of moxifloxacin hydrochloride (BAY 12-8039) rather than moxifloxacin, despite the contemporaneous record that he had no such preference, that he thought BAY 12-8039 and moxifloxacin were the same thing, and the scientific principle that there is no difference between solutions made with BAY 12-8039 and moxifloxacin.

Teva's enablement argument is nothing more than an attempt to reverse the burden of proof, as it essentially argues that Alcon has not proven its claim is enabled. Of course, the law requires no such thing. In any event, there is no evidence whatsoever that a POOS (under either party's definition) could not practice the claimed invention without undue experimentation; to the contrary, the evidence shows that this would be a trivial task.

Finally, Teva's written description argument is baseless. Teva's premise that the '830 patent does not disclose a composition without a separate preservative is demonstrably wrong, as the patent specification makes clear that a preservative is not always required and even includes an example that does not contain a separate preservative.

The evidence and the law are clear: Teva has failed to prove that claim 1 is invalid.

ARGUMENT

I. CLAIM 1 OF THE '830 PATENT WAS NOT OBVIOUS

A. The Selection of Moxifloxacin Is the Critical Issue

Claim 1 of the '830 patent claims a topical ophthalmic composition containing moxifloxacin. Whether it would have been obvious for a POOS to select moxifloxacin for use in an ophthalmic composition is the core issue in the case.

That this is the critical question is amply demonstrated by application of two of the four *Graham v. John Deere Co.* factors – the scope and content of the prior art and the differences between the invention and the prior art. 383 U.S. 1, 17-18 (1966). There is no dispute that the prior art included (1) literature regarding the treatment and prevention of ophthalmic infections, (2) the state of the art products Ciloxan® and Ocuflox® (topical ophthalmic compositions respectively containing ciprofloxacin ("cipro") and ofloxacin), and (3) innumerable references disclosing antibiotics from various classes, including hundreds each year disclosing quinolone antibiotics. Trial Transcript ("Tr.") 72:7-73:23 (Taylor); 263:25-264:1 (Allen); 887:24-889:11, 898:15-25 (Zhanel); PTX 194-D. There likewise is no dispute that the only difference between the prior art and the claimed invention is the active ingredient – the state of the art compositions contained cipro and ofloxacin, while the claimed compositions contain moxifloxacin. D.I. 107 ("Teva Br.") at 32-33; Tr. 196:7-214:18; 220:10-223:5 (Allen); DTX 4013-16. Critical to the invention, therefore, is the choice to use moxifloxacin in a topical ophthalmic composition in

place of the antibiotics used in the prior art. *Graham*, 383 U.S. at 17-18; *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1743 (2007); 35 U.S.C. § 103(a) (precluding patent if "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a" POOS).

The '830 patent itself confirms this. The patent describes the "state of the art in the field of ophthalmic pharmaceutical compositions," including Ciloxan® and Ocuflox®. PTX 5 at 1:22-36. It then identifies the problem to which it is directed and the solution: the "need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens" – thus making clear that the invention is "based on" selecting an antibiotic that would be better than existing compositions. *Id.* at 1:47-53.

Drs. Alfonso and Zhanel, who were working to evaluate antibiotics for potential use in ophthalmic compositions in 1998, testified that the patent accurately identifies the need in the field at that time. Tr. 831:8-834:4, 1028:17-1030:1 (Zhanel); 375:9-15, 404:8-405:25 (Alfonso). And Teva's expert Dr. Allen, despite initially arguing that the '830 patent relates to formulating compositions rather than selecting an active ingredient, ultimately agreed that it addresses the need for more effective antibiotic compositions and that its proposed solution is to select moxifloxacin for ophthalmic use. Tr. 247:14-259:14. Contrary to Teva's suggestion, there is no indication that the '830 patent addresses a problem in formulating ophthalmic compositions or optimizing excipients (inactive ingredients) after an active ingredient is selected – indeed, there is no evidence that any such problem existed. Tr. 836:4-7 (Zhanel); 258:23-259:14 (Allen).

The salient question for obviousness, therefore, is whether the prior art as a whole suggested or provided a reason for the POOS to select moxifloxacin for use in an ophthalmic

composition in place of the antibiotics used in prior art compositions. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1359, 1357-62 (Fed. Cir. 2007) (no obviousness absent proof that "prior art would have led to the selection of compound b" as a starting point); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364-65 (Fed. Cir. 2008).

Teva seeks to recast the obviousness inquiry so as to avoid the question of whether selecting moxifloxacin for ophthalmic use was obvious. That is no doubt because its expert, Dr. Allen, admittedly lacks the expertise to address this issue. Dr. Allen readily admitted that:

- he was "not testifying it would have been obvious to select moxifloxacin to put into an ophthalmic composition in 1998," Tr. 244:10-245:8 (emphasis added);
- he assumed for purposes of his opinion that moxifloxacin already had been selected as the active ingredient in an ophthalmic composition, Tr. at 243:21-245:16;
- he did not consider the prior art regarding moxifloxacin and other potential active ingredients, Tr. 277:4-280:19, 261:23-262:13, 270:22-271:20; 339:15-344:25; and
- neither he nor his POOS had the experience or expertise to select an antibacterial agent for an ophthalmic formulation, Tr. 240:7-242:11; 245:17-247:14, 264:14-265:23.

Dr. Allen's opinion thus is that if one assumes that it has already been decided that moxifloxacin should be used in a topical ophthalmic composition, then a topical ophthalmic composition containing moxifloxacin is obvious (because it would be easy to prepare). Dr. Allen studiously avoids answering the question that is actually relevant: whether "it would have been obvious to select moxifloxacin to put into an ophthalmic composition in 1998."

B. The POOS Possesses Skills and Experience in the Fields of Microbiology and the Treatment and Prevention of Ophthalmic Infections

As explained in Alcon's infringement brief (D.I. 93 at 4-6), the POOS is a microbiologist and/or ophthalmologist who—like the inventors and artisans who were investigating potential

topical ophthalmic compositions—possesses the skills, knowledge, and experience necessary to understand the problem to which the '830 patent is directed and select an active ingredient for ophthalmic use. PTX 2018 (listing the qualifications of the POOS). This person also would have skills in formulating compositions. *Id.*; Tr. 991:14-993:22 (Zhanel); 412:7-9 (Alfonso).

Because Teva refuses to acknowledge that the selection of moxifloxacin as the active ingredient is part of the '830 patent's invention, it proposes a different POOS. Tr. 245:5-16 (Allen). Teva asserts that the POOS is a pharmaceutical scientist who formulates ophthalmic compositions but lacks knowledge and expertise regarding quinolones, microbiology, toxicity, the treatment of ophthalmic infections, and the needs for ophthalmic compositions—in short, all the skills necessary to select the compositions' active ingredients. Tr. 245:17-247:14; 234:21-239:12; 240:7-243:8; 264:14-265:23; 366:24-367:16 (Allen); 408:8-410:25 (Alfonso). As both the evidence and law demonstrate, Teva's definition is simply wrong.

1. Teva Misapplies the Standard for Determination of the POOS

Teva and Alcon agree on the six-factor test for defining a POOS. Teva Br. at 24; D.I. 93 at 4; *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007). Teva misapplies this test, however, in hopes of convincing the Court to adopt its misguided POOS definition.

The first factor is the educational level of the inventors. Recognizing that this factor favors Alcon's definition, Teva posits that the Court should ignore the inventors' backgrounds as microbiologists because they did not perform any microbiological tests in connection with their invention. Teva Br. at 24. That is baseless – it incorrectly assumes that microbiologists only practice in that field when conducting tests, as opposed to (for example) analyzing data, evaluating needs in the field of treating and preventing ophthalmic infections, and assessing compounds to select an active ingredient. Dr. Stroman (unsuccessfully) engaged in these

evaluations for eight years before the invention of the '830 patent. Tr. 565:8-567:9; 571:2-573:6. The inventors' backgrounds are entirely consistent with Alcon's POOS. The expertise of other Alcon employees in optimizing a formulation for commercial use does not support Teva's definition. Teva Br. at 24-25. To the contrary, that these formulators are not inventors and that such optimization is nowhere reflected in the '830 patent further reflects that the patent is directed to selecting an active ingredient, not the later step of optimizing formulations. Tr. 256:1-257:9 (Allen); 673:16-675:11 (Stroman); 411:14-412:6 (Alfonso); 835:18-839:7 (Zhanel).

Teva has no real response to the facts that the problem in the art related to the need for a composition containing an antibiotic that would be more effective than existing antibiotics against the key ocular pathogens (factor 2), and that the individuals who sought to solve that problem were sophisticated microbiologists and/or ophthalmologists (factors 5 and 6). Tr. 375:9-15; 404:8-407:6; 394:6-395:11; 403:2-18 (Alfonso); 831:8-835:17; 1028:17-1030:1 (Zhanel); 247:14-259:14 (Allen). Selection of an appropriate compound to solve the problem in the field required a thorough understanding of the problem, and expertise in the evaluation of pharmacokinetic, pharmacodynamic, and toxicological data and the assessment of the relative expected risks and benefits associated with ophthalmic use of a potential compound—the very skills embodied in Alcon's definition of a POOS and excluded by Teva's. Tr. 406:1-410:25 (Alfonso); 836:8-837:10 (Zhanel) (without expertise of Alcon's POOS, one could not determine whether potential treatment would be more effective and less prone to develop resistance). It is thus no coincidence that Drs. Alfonso, Stroman, and Zhanel all were involved in decisions regarding whether to use various antibiotics ophthalmically in the 1990s and testified uniformly that microbiologists and ophthalmologists made those decisions, without input from formulators. Tr. 403:2-18, 411:14-412:6 (Alfonso); 834:5-839:7 (Zhanel); 615:22-617:3 (Stroman).

By contrast, Dr. Allen and his POOS plainly lack the expertise to understand the problem in the field, let alone assess potential solutions. Dr. Allen agreed that his POOS is not an expert in microbiology or ophthalmology, lacks the ability or experience to select an active ingredient for ophthalmic use, and lacks familiarity with the history of quinolones, the location of infections that required better therapy, and the very needs in the field of ophthalmology to which the patent is explicitly addressed. Tr. 240:7-242:11; 245:17-247:14, 264:14-265:23, 366:24-367:16. He further admitted that such knowledge is relevant in the selection of a compound to use in an ophthalmic composition—a selection that he himself has never made in his decades of work in formulation research. Tr. 234:21-236:17; 264:14-265:23. To define the POOS to have a skill set so limited that it precludes even understanding the problems in the field or evaluating potential solutions is contrary to logic and law. *Daiichi*, 501 F.3d at 1257.[1]

Ignoring the actual problem identified in the field and the patent, Teva relies on portions of the specification that refer to formulating the compositions. Teva Br. at 27-29. Those portions simply reflect that the compositions must be appropriately formulated, not that there was a problem relating to formulation. And Teva's reliance on the absence of formulation details to contend that the patent must be directed to a formulator who can "fill in the gaps" both (as discussed in Section IV) incorrectly assumes that ophthalmologists and microbiologists are unable to do so and turns logic on its head. That a patent lacks disclosure regarding a given field suggests that it is not the subject of the claimed invention, not that it is the subject. In any event, Teva's argument is a red herring, as both parties agree that a POOS would have formulation

[1] Belatedly recognizing the deficiency of its definition, Teva argues that it does not exclude a microbiologist. Teva Br. at 25 n.11. The testimony Teva cites indicates that formulators take a microbiology course, but "they would not be an expert in microbiology." Tr. 246:9-18. There is no evidence that Teva's POOS would have the expertise to select a compound for ophthalmic use, and ample evidence to the contrary. Tr. 836:8-837:10 (Zhanel); Tr. 406:1-410:25 (Alfonso). Dr. Allen admittedly lacked such expertise.

experience. PTX 2018; Tr. 991:14-993:22 (Zhanel); 412:7-9 (Alfonso).

Application of the remaining factors—prior art solutions and the rapidity of innovations in the field—resolves any doubt that Alcon's definition is correct and reaffirms Teva's fundamental misconception of the '830 patent's invention. Teva properly identifies the prior art solutions, such as Ciloxan®, but posits without support that they resulted only from "formulating an ophthalmic composition of a known fluoroquinolone antibiotic," as if new products can simply emerge from rote formulation of any known quinolone, rather than the selection of an appropriate active ingredient based on clinical needs and microbiological data. Teva Br. at 25-27. Teva's simplistic view that ophthalmic use follows routinely from publication of an antibiotic or its use in a tablet is simply wrong. The undisputed testimony was that hundreds of new quinolones—one of many classes of antibiotics—were published every year, and many were investigated and even clinically tested for various systemic uses (especially respiratory tract infections ("RTI")) after the launch of cipro and ofloxacin. Tr. 72:7-73:23 (Taylor); 263:25-264:17 (Allen); 898:15-25, 887:24-889:11 (Zhanel); PTX 2025. Were Teva correct that artisans simply "formulated . . . ophthalmic composition[s]" of "known fluoroquinolone antibiotic[s]," and that "development of topical ophthalmic dosage forms containing an antibiotic" follows rapidly after the development of other dosage forms like tablets, then hundreds of ophthalmic quinolones would have been investigated and developed between the launches of Ciloxan® and Ocuflox® in the early 1990s and the priority date (when these products remained the state of the art). There were none. Tr. 948:16-949:17; 1118:25-1119:8, 1138:8-19; 963:12-15 (Zhanel); 195:3-9 (Allen); 459:8-22 (Alfonso); PTX 2025 (non-exhaustive list of quinolones developed systemically). The contemporaneous actions of scientists who were working to solve the problems in the field in 1998 flatly contradicts Teva's argument; skilled artisans did not pursue

ophthalmic compositions of even the most promising quinolones in the 1990s. Tr. 963:12-15 (Zhanel); 419:11-420:2, 491:7-23 (Alfonso) (quinolones "were not really on the radar screen in terms of looking for an appropriate antibacterial" for ophthalmic use in 1998); PTX 2025.

Daiichi v. Apotex, on which Teva relies, supports Alcon not Teva. In considering a patent to an antibiotic ear treatment, the *Daiichi* court defined the POOS as a "person engaged in developing pharmaceutical formulations and treatment methods" or a medical specialist in ear treatments (an otologist)—not a formulator as Teva (at 27) misleadingly suggests. *Daiichi*, 501 F.3d at 1256-58. The court relied on (1) the inventors' educational backgrounds (without regard to what portion of it they used or what degrees their colleagues possessed), (2) the backgrounds of other artisans "working in the same field as the inventors," (3) the medical problem the patent on its face sought to solve (not the field to which the gaps in the patent pertain), and (4) that one party's POOS lacked the expertise in microbiological testing and analysis required to develop the claimed treatment. *Id.* *Daiichi*'s definition conflicts with Teva's, both because Teva omits the skills of a person familiar with treating and preventing ophthalmic infections and because *Daiichi's* "person engaged in developing pharmaceutical formulations" refers to one "engaged in the research and development of antibiotics," not pharmacists who prepare formulations after others select the active ingredient. *Id.* at 1257. By contrast, *Daiichi* is entirely consistent with Alcon's POOS. *See Boehringer Ingelheim Int'l v. Barr Labs., Inc.*, 2008 WL 2553237, *13-14 (D. Del. June 26, 2008) (rejecting POOS definition that excluded expertise in inventors' field).

2. Alcon's Definition Is Easily Understood

Having no substantive support for its POOS definition, Teva retreats to a grammatical argument that Alcon's POOS definition "us[es] the indefinite (and/or) connector" and thus "fails to provide the Court with a cogent lens through which to view the patent and the prior art." Teva Br. at 29. Teva contends that by using the connector "and/or," Alcon's definition does not

specify whether the POOS is a microbiologist and ophthalmologist, or a microbiologist or ophthalmologist, and that somehow this means that the testimony of one or both of Alcon's experts should be ignored in its entirety. *Id.* at 29-30. Not surprisingly, Teva cites no authority to support its erroneous theory that the use of "and/or" renders a POOS definition improper. Any person fluent in the English language understands the meaning of "and/or"—either or both of the connected items may be included. And that this phrase is appropriately used in defining the POOS in a patent case is beyond debate; courts regularly and routinely employ it, including where Teva itself proffered a definition containing "and/or" to this very Court.[2]

3. Drs. Zhanel and Alfonso Are Competent to Testify Regarding Validity

Building from its faulty grammatical objections, Teva seeks to avoid the substance of Drs. Zhanel and Alfonso's unrebutted testimony by suggesting that their testimony should be ignored because their backgrounds do not match the hypothetical POOS's exactly. Teva Br. at 30-31, 34. Teva's argument has no basis in either fact or law.

The fundamental issue for defining the POOS is what skill set this hypothetical person would have, not what precise degree he or she would have hypothetically earned. Alcon's definition describes a skill set that scientists engaged in investigating and using products that treat and prevent ophthalmic infections would—and actually did—have. PTX 2018. For

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[2] *See, e.g.*, *Merck & Co. v. Teva Pharms. USA, Inc.*, 228 F. Supp. 2d 480, 501 (D. Del. 2002) (adopting Teva's proposed definition, which included "and/or"); *Merck & Co. v. Teva Pharms. USA, Inc.*, 288 F. Supp. 2d 601, 626 (D. Del. 2003) (court combined Merck and Teva's definition of POOS: "an individual who would have an M.D. and/or Ph.D. and was working in the field of and doing research on osteoporosis") (POOS finding *affirmed* in *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Glaxo Group Ltd. v. Teva Pharms. USA, Inc.*, 2004 WL 1875017, at *2 (D. Del. Aug. 20, 2004) (POOS "is one with an advanced degree in pharmacology and/or a medical doctor with experience in clinical pharmacology"); *Pressure Prods. Med. Supplies, Inc. v. Enpath Med., Inc.*, 2008 WL 744250, at *1 n.2 (E.D. Tex. Mar. 19, 2008) (POOS is a "biomedical engineer or biomedical device designer and/or manufacturer with at least five years of experience working in the field").

example, familiarity with the nature of the infections that required better products to treat and prevent, knowledge of the shortcomings of existing therapies, and experience in evaluating data and the risks and benefits associated with potential therapies are all necessary to understand the needs in the field and to determine whether a potential therapy might meet them. Tr. 406:1-410:25, 392:3-395:11, 371:13-375:15, 403:2-18; (Alfonso); 829:4-24, 834:5-836:23 (Zhanel). Individuals with that background generally have degrees and training in microbiology and/or ophthalmology—whether it is both, which one it is, or what particular degrees they have (the focus of Teva's argument) is utterly inconsequential. Tr. 441:25-445:20, 484:25-485:20 (Alfonso); 988:18-991:13 (Zhanel). For example, Dr. Alfonso, an ophthalmologist, heads a microbiology laboratory in which he tests potential antibiotic therapies. Tr. 371:13-375:8. Dr. Zhanel is formally a microbiologist, but he consults with physicians regarding the treatment of ophthalmic infections. Tr. 826:10-829:24. Both – and many others who shared their skill set – were intimately involved in research in the field. *Id.*; Tr. 371:13-375:7; 485:21-486:10 (Alfonso). Alcon's definition thus appropriately takes into account the unassailable fact that individuals with different formal degrees work in a given field and develop a particular skill set. Here, consistent with who was actually engaged in solving the relevant problems, the POOS is a microbiologist, an ophthalmologist, or both, who has the relevant background and experience.

Moreover, the Federal Circuit has already rejected Teva's legal argument that Dr. Zhanel and/or Dr. Alfonso cannot testify because they are "not a POOS." When faced with this same argument for exclusion of an expert's testimony, the Federal Circuit held that "[o]f course that objection is meritless. The 'person of ordinary skill in the art' is a theoretical construct used in determining obviousness under § 103, and is not descriptive of some particular individual." *Endress + Hauser, Inc. v. Hawk Measurement Sys. Pty. Ltd.*, 122 F.3d 1040, 1042 (Fed. Cir.

1997). Because the POOS is a hypothetical person – not an actual individual whose background a witness must match identically – Teva's notion that Drs. Zhanel and Alfonso's testimony should be ignored unless their backgrounds perfectly match that of the POOS is flatly wrong.[3]

C. The Prior Art As a Whole Taught Away from Selecting Moxifloxacin for Use in an Ophthalmic Composition

1. The Needs and Requirements in the Field

Column 1 of the '830 patent clearly identifies the problems and needs in the field of treating and preventing ophthalmic infections, to which the invention is directed:

> There is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens.

A POOS would have understood this statement to reflect the common understanding that dangerous, sight-threatening infections inside the eye caused by the "key ophthalmic pathogens" *staph* and *pseudomonas* were increasingly resistant to the existing Ciloxan® and Ocuflox® therapies and thus difficult (if not impossible) to treat and prevent, and that there was a need to address this problem. Tr. 375:9-15; 381:12-387:14, 404:8-405:25 (Alfonso); 566:6-567:9 (Stroman); 831:8-834:4, 843:18-845:6 (Zhanel).

By contrast, there was no need for a product that only was able to treat surface infections, such as conjunctivitis. The existing products adequately treated conjunctivitis, which unlike intraocular infections, often resolves without treatment and is not serious or sight-threatening. Tr. 389:19-391:5; 410:10-25 (Alfonso); 844:18-845:6 (Zhanel); 566:21-567:9 (Stroman). Thus, artisans were not attempting to develop new treatments for conjunctivitis, and a POOS would

[3] If anything, the cases on which Teva relies demonstrate that Dr. Allen is the expert whose testimony should be severely discounted, as he testified regarding issues of microbiology and ophthalmology, despite his repeated admissions that this is "not my field." *Merck & Co. v. Teva Pharms., USA, Inc.*, 347 F.3d 1367, 1371-72 (Fed. Cir. 2003); Tr. 331:1-333:5; 348:5-350:10.

have had no reason to make a composition that was expected to treat conjunctivitis but not improve on the existing treatments for the intraocular infections that posed a significant problem. *Id.*; Tr. 237:17-238:14; 259:15-261:2 (Allen) (disclaiming any knowledge about whether there was a need regarding treatment of surface infections). A POOS reading the patent would understand that "there was no need for a new drug for conjunctivitis," and the patent is "very clear" that it is directed to the need for a composition to treat and prevent intraocular infections caused by *staph* and *pseudomonas*. Tr. 1018:23-1022:7 (Zhanel).[4] In any event, a POOS in 1998 would have had no reason to use moxifloxacin to treat conjunctivitis. *See* Section I.C.5.

To address the actual problem in the field, the art demanded a "more effective" antibiotic, which a POOS would have understood to require that an antibiotic: (1) be more active than cipro against *staph* and at least as active as cipro against *pseudomonas*, so it could treat and prevent intraocular infections caused by all important pathogens, (2) avoid the "development of resistance by those pathogens," especially *pseudomonas*, and (3) be at least as safe as cipro and ofloxacin. Tr. 381:12-388:14; 392:3-393:15; 404:8-405:25 (Alfonso); 831:8- 834:4; 839:25-845:6 (Zhanel); PTX 2019. Dr. Allen did not dispute these requirements and admitted that he lacked expertise in and knowledge of problems "faced by ophthalmologists in 1998 regarding the treatment and prevention of infections in the eye." Tr. 237:17-242:5. The evidence showed that a POOS would have expected a moxifloxacin composition to meet none of these requirements.

[4] Teva relies heavily on the fact that Vigamox®, like virtually every topical ophthalmic antibiotic, was indicated to treat conjunctivitis when it was approved by the FDA years after the priority date. Teva Br. at 21. However, a POOS would not have had reason to pursue a topical ophthalmic composition unless it had the ability to treat and prevent intraocular infections, including those caused by *pseudomonas*, irrespective of whether it could treat conjunctivitis. Alcon's product is indicated for conjunctivitis due to the exigencies of the regulatory process (such as difficulties enrolling patients in studies) that have no pertinence to the obviousness inquiry, not because of a need to develop a new conjunctivitis drug. Tr. 566:21-569:14 (Stroman); 541:17-543:24 (Alfonso); 1022:8-1023:10; 893:4-22 (Zhanel).

On the contrary, the prior art consistently taught away from using moxifloxacin in an ophthalmic composition. 980:14-984:4; 876:12-879:20; 843:18-845:6 (Zhanel); 490:18-491:23 (Alfonso).

2. Moxifloxacin Lacked the Requisite Activity

Because the identity of the pathogen causing an infection is not known when prophylaxis or treatment is initiated, it was "very important" that antibiotics in ophthalmic compositions have a "broad spectrum of coverage" against all important ocular pathogens; a coverage gap "open[s] the door to those bacteria that were not being covered," which may quickly cause "significant damage." Tr. 388:15-389:18 (Alfonso); 273:19-275:10 (Allen); 878:10-880:6 (Zhanel). As between *staph* and *pseudomonas*, a lack of activity against *pseudomonas* was considered far more dangerous, since it is "the most threatening" ocular pathogen. Tr. 566:6-20 (Stroman). The need to "come up with better coverage for *pseudomonas* than what the currently available fluoroquinolones could provide" was "the hot topic" in the field. Tr. 392:3-393:15 (Alfonso).

In evaluating a compound for potential ophthalmic use, a POOS would have compared its activity against *pseudomonas* and *staph* to that of cipro, the "standard to which all quinolones were compared, especially in the ocular field where *pseudomonas* is the critical pathogen." Tr. 856:14-858:16; 860:3-13 (Zhanel); PTX 137 (comparing activity of quinolones to cipro, not ofloxacin), 1124 (same). Cipro was known to have "tremendous activity" against *pseudomonas*, but not very good activity against *staph*. Tr. 856:14-857:14 (Zhanel). Artisans thus sought, and a POOS only would have interest in, compounds that improved on cipro's *staph* activity while at least maintaining its *pseudomonas* activity; a POOS would "absolutely not" have had interest in a compound that achieved the former, but not the latter. *Id.*; Tr. 402:6-18; 416:11-23 (Alfonso).

The prior art repeatedly confirmed that moxifloxacin was exactly such an undesirable compound for ophthalmic use, showing – in the Woodcock article, the Fass article, and the Bayer poster on which Teva relies – that, while it was more active against *staph*, moxifloxacin was

eight times less active than cipro against *pseudomonas*, the most feared ocular pathogen. Tr. 416:24-418:20 (Alfonso); 857:21-862:19 (Zhanel); 348:5-350:10 (Allen), PTX 137, 225, 1098. Teva has no contrary evidence, simply relying on the '942 patent to contend that moxifloxacin is "active against a very broad spectrum of microorganisms," Teva Br. at 10, even though that patent has no such disclosure directed to moxifloxacin, has no data at all about moxifloxacin, and has no data about any compound's *pseudomonas* activity. PTX 3; Tr. 967:8-971:25 (Zhanel); 280:20-282:25, 302:18-306:6 (Allen); Section II.B. The notion that a POOS would interpret this bald statement in the '942 patent to trump later publications that actually provide data showing moxifloxacin's *pseudomonas* activity is simply spurious. Tr. 967:8-971:25 (Zhanel).

Dr. Allen sought to dismiss moxifloxacin's inferior *pseudomonas* activity. In his view, an eight-fold activity difference in a MIC test is "not meaningful" and "in a similar ballpark" because it is "within one dilution," which he understands to be one order of magnitude (e.g., .1 to 1) – despite admitting four times that analyzing MIC data is "not my field" and that he does not evaluate MIC data as part of his professional life, ostensibly except when he testifies in court. Tr. 331:1-333:5; 348:5-350:10; Tr. 228:7-230:5; 236:18-237:16; PTX 1098.

As Dr. Zhanel—who has compared compounds using MIC tests "every single day . . . for the last 20 years" and runs a laboratory that has performed "well over 100,000" MIC tests—explained, Dr. Allen is wrong. Tr. 853:18-854:1. The internationally-accepted standard is that a dilution step reflects a two-fold difference in activity (i.e., .5 vs. 1), not a ten-fold "order of magnitude" difference. Tr. 858:17-860:2 (Zhanel). And the eight-fold difference (three dilution steps) in *pseudomonas* activity between moxifloxacin and cipro is "hugely significant," and no one skilled in the art of microbiology would conclude otherwise. Tr. 860:14-861:1. A person with experience in microbiology would have looked at the available data for moxifloxacin and

concluded that "I'm gaining on . . . *Staph. aureus*, but I'm losing significantly on the *pseudomonas aeruginosa* side. That's not good." Tr. 871:6-24; 857:21-862:19 (POOS would have found loss of activity against the "more important ocular pathogen" "very worrisome") (Zhanel). The prior art thus suggested that moxifloxacin would have been unable to treat ocular *pseudomonas* infections, and a POOS therefore would not have had interest in moxifloxacin for topical ophthalmic use, notwithstanding its *staph* activity. *Id.*; Tr. 388:15-389:18; 398:25-399:2; 402:6-18; 416:11-23 (Alfonso); 271:21-275:10 (Allen); 876:12-880:6; 980:14-981:7 (moxifloxacin was "significantly less active against *pseudomonas*, . . . and if you didn't cover it, you had no hope of being an ophthalmic composition antimicrobial.") (Zhanel).[5]

The contemporaneous record confirms that scientists did not regard moxifloxacin as a suitable candidate to treat and prevent infections in tissues—such as the eye—where *pseudomonas* was prevalent. "[D]ifferent pathogens target different tissues," so an antibiotic that provides a broad spectrum therapy for infections in one tissue may be entirely unsuitable for another. Tr. 879:21-880:6 (Zhanel). For instance, while *pseudomonas* "loves water" and infects the eye, it does not cause community acquired respiratory tract infections, in which *s. pneumonia* and *h. influenza* are the most important pathogens. Tr. 847:10-849:4 (Zhanel). Because no compound can treat all infections, microbiologists and medical specialists analyze a compound's activity to determine the particular types of infections it may be useful in treating. Tr. 834:5-835:17; 969:20-970:14 (Zhanel); 394:6-395:11 (Alfonso). The literature was replete with such analysis of moxifloxacin, and there was not a single suggestion that it would be useful to treat or prevent ophthalmic infections. For example, the Dahloff article notes that moxifloxacin

[5] That a POOS would not have been interested in a compound that was less active than cipro against *pseudomonas*, even if it had enhanced activity against *staph*, renders utterly irrelevant Teva's repeated reliance on moxifloxacin's activity against *staph*. *See* Teva Br. at 18, 19, 35.

enhances or retains the potency of cipro, except against *pseudomonas*, and then concludes that the "antibacterial spectrum . . . indicates that it might be a very useful quinolone for treating respiratory, genitourinary, intra-abdominal and skin and skin structure infections"—all non-ocular infections characterized by not being caused by *pseudomonas*. PTX 1124 at 423-24; Tr. 552:2-553:3 (Alfonso); 875:14-876:11 (Zhanel); *see also* PTX 194-D at 774 (indicating moxifloxacin and other quinolones were being developed to treat RTIs); Tr. 849:5-850:18 (Zhanel); DTX 161 at 655 (noting moxifloxacin's diminished activity against *pseudomonas*), Tr. 1138:20-1139:17 (Zhanel); PTX 225; Tr. 953:22-955:2 (Zhanel); 547:5-548:5 (Alfonso); 1127:20-1129:7 (Zhanel). Viewed as a whole, the prior art disclosed

> overwhelming data that, microbiologically, moxifloxacin was inferior, significantly less active than ciprofloxacin [against] *Pseudomonas aeruginosa*. And that is why moxifloxacin was being developed for non-pseudomonal community-acquired respiratory tract infections. . . . [T]he art was teaching away from pseudomonal infections. It says anywhere you think *pseudomonas* is an issue, don't go there. And that is why all the conclusions that were available in September '98 were talking about non-pseudomonal infections such as community-acquired respiratory tract infections. That was clear.

Tr. 1017:6-1018:6, 1044:23-1045:17 (Zhanel); *see also* Tr. 416:11-23, 546:5-547:4 (Alfonso).

3. A POOS Would Have Expected Ophthalmic Moxifloxacin To Enhance *Pseudomonas* Resistance

It was "common knowledge" that the resistance problem identified in the patent was a "class effect," meaning that if a bacterial strain was resistant to one quinolone, it would become resistant to "all the other fluoroquinolone[s]." Tr. 398:14-399:2; 419:11-420:2 (Alfonso); 885:4-25 (Zhanel). It was also well understood in the context of quinolones and *pseudomonas* that because "resistance occurs when you use an antimicrobial [and] you don't kill the pathogen, . . . using a drug that is weaker than other agents in the class," and thus less likely to kill the pathogen, "drive[s] resistance to not just this drug, but all of the drugs in that class. And this is a huge issue." Tr. 886:1-887:23; 852:20-853:13 (Zhanel); 398:14-399:2 (Alfonso). That is

exactly why, contrary to Teva's suggestion, the POOS would not have been interested in a drug with *pseudomonas* activity comparable to ofloxacin's (which was worse than cipro's) – use of ofloxacin was widely understood in 1998 to be driving *pseudomonas* resistance to all quinolones. Tr. 874:16-875:8; 886:1-887:23 (Zhanel). Ofloxacin was viewed as part of the problem in 1998, which is why cipro was the relevant activity comparator. Tr. 856:8-23; 860:3-13; 863:7-15.

Therefore, a POOS in 1998 would have expected that using moxifloxacin (which was just as bad as ofloxacin, Tr. 873:23-874:15, 1014:10-24) would enhance *pseudomonas* resistance to all quinolones, including cipro. Tr. 876:12-879:20; 889:12-892:10; 839:25-843:13 (Zhanel). Dr. Allen agreed that "quinolone resistant strains of *pseudomonas* were a major concern in 1998," Tr. 271:21-273:4, and as Dr. Zhanel testified, a POOS would have concluded that use of an ophthalmic moxifloxacin composition would "predispose patients to clinically failing and, perhaps more importantly, if I don't kill the organism, I'm going to drive quinolone resistance through the roof. I'm going to take the most important problem in ocular infectious diseases in September 1998, and by using a drug that won't kill *pseudomonas*, I'm going to make the problem worse." Tr. 876:12-877:24; 889:22-890:10; 897:6-21; 880:7-885:3; PTX 184-D; PTX 189. It is no surprise that artisans were not interested in quinolones that, like moxifloxacin, were less active than cipro against *pseudomonas*. Tr. 889:12-21 (Zhanel); 398:15-399:2 (Alfonso).

Contrary to the unrebutted expert testimony, Teva argues that moxifloxacin was "known in September 1998 to have a better resistance profile than ciprofloxacin." Teva Br. at 18-19. That is wrong. Dr. Zhanel testified repeatedly that the prior art contained no evidence to suggest that moxifloxacin would solve the *pseudomonas* resistance problem and ample evidence that it would have "driven *pseudomonas* resistance through the roof." Tr. 981:8-984:4; 826:8-827:7; 890:11-16; 1017:3-1018:22. Undeterred, Teva relies on a single article (PTX 1124), which

(expurgating Dr. Zhanel's contrary interpretation) it interprets to disclose that "resistance to moxifloxacin HCl in *Pseudomonas aeruginosa* . . . emerged less rapidly than resistance to ciprofloxacin." Teva Br. at 19. The article says no such thing. It refers to resistance data for *S. pneumoniae* in figure 8 showing a sharp rise in moxifloxacin's MIC and states that "[a]nalogous data were obtained for" *pseudomonas*. While Teva's counsel, without evidentiary support, reads this statement to be encouraging, as Dr. Zhanel explained, given moxifloxacin's activity against *pseudomonas*, the POOS would have read the article to indicate that *pseudomonas* resistance to moxifloxacin would, in fact, emerge rapidly. Far from encouraging, a POOS would have considered the article's disclosure "scary," "frightening" and "disturbing for moxifloxacin and *pseudomonas*." Tr. 1045:23-1048:14; 1139:18-1142:12 (Zhanel); PTX 1124 at 422. Indeed, the article's list of infections for which moxifloxacin may prove useful omits those caused by *pseudomonas*. PTX 1124 at 424; Tr. 552:2-553:3 (Alfonso); 875:14-876:11; 1141:15-1142:12 (Zhanel). Unable to rebut Dr. Zhanel's interpretation of how a POOS would interpret the article, Teva simply ignores it and argues instead an unsupported and baseless contrary interpretation.

4. The *Pseudomonas* Resistance Problem Taught Away from Selecting Moxifloxacin

In 1998, artisans in the field sought to solve the problem of *pseudomonas* resistance by focusing on classes of antibiotics other than quinolones. Tr. 887:24-889:11; 885:4-25 (Zhanel); 396:24-398:7 (Alfonso); PTX 1099. In light of the class resistance problem, "continuing to look at a fluoroquinolone was really a step back," and accordingly, quinolones "were not really on the radar screen in terms of looking for an appropriate antibacterial" for ophthalmic use in September 1998. Tr. 419:11-420:2; 490:18-491:23 (Alfonso); *see also* 887:24-889:11 (Zhanel).

Moreover, a POOS who even considered a quinolone for ophthalmic use would not have selected moxifloxacin. Numerous other quinolones, including clinafloxacin, grepafloxacin, and

olamufloxacin, possessed the requisite activity profile of enhanced *staph* activity and at least equivalent *pseudomonas* activity compared to cipro that moxifloxacin lacked. Tr. 862:25-870:18; 947:9-25 (Zhanel); 350:11-353:19 (Allen); PTX 163 at 25-26; PTX 194-D at 768; PTX 1098. Moxifloxacin was thus far from the most desirable compound to select.

5. The Risk to Benefit Ratio Taught Away from Selecting Moxifloxacin

Both parties' experts agreed that the toxicity of a potential ophthalmic composition is assessed by weighing its expected therapeutic advantages against the toxicological risks. Tr. 177:19-178:2 (Allen); 894:15-895:5 (Zhanel). A POOS would have expected ophthalmic moxifloxacin to be "less effective" than Ciloxan®. Tr. 897:6-21; 981:8-984:4 (Zhanel); *see also* Section I.C.2-4. In determining acceptable risk, a POOS would have focused on the expected predominant use of the composition, which in this case is prophylactically in uninfected cataract and Lasik surgery patients. Tr. 387:15-24 (Alfonso); 845:7-16; 895:6-896:5 (Zhanel). Given this expected prophylactic use in which the likelihood of an infection is extremely low, and the excellent safety record of the existing compositions, a POOS would have had a "risk tolerance [of] zero" and only considered an antibiotic for ophthalmic use that was as safe as ofloxacin and cipro. Tr. 961:24-963:15; 895:6-896:5 (Zhanel); 391:12-25; 399:3-400:10 (Alfonso).

By 1998, quinolones were considered "the most toxic antimicrobial class that we had seen." Tr. 931:1-17; 940:19-941:3 (Zhanel); 420:8-18 (Alfonso). The general rule was that "the more powerful the quinolones are at killing bacteria, the more powerful they are at killing people," and the expectation with regard to every quinolone was that it would be toxic; cipro and ofloxacin were the rare exceptions. Tr. 897:22-898:14; 829:25-830:11; 933:5-7 (Zhanel). While the exact toxicity that a new quinolone would exhibit was unpredictable—be it liver toxicity, blood cell lysis, cardiac issues, or something else—it was predictable and expected that any new quinolone would cause toxicity that would render it unsuitable for ophthalmic use. *Id.*; Tr.

948:16-949:17; 911:1-915:13; 927:25-934:7; 938:5-23; 1138:8-19 (Zhanel); PTX 2025. The contemporaneous actions of artisans confirm this: while hundreds of new quinolones were published each year, and numerous post-cipro quinolones were pursued in clinical trials for life-threatening, non-ocular infections, by September 1998 not one had even entered a clinical trial for ophthalmic use. Tr. 948:16-949:17; 1138:8-19; 963:12-15; 908:21-23; 940:1-5 (Zhanel); PTX 2025 (non-exhaustive list of more than 30 post-cipro quinolones, all of which proved toxic, and none of which were used ophthalmically); Section I.B.1.

A POOS would have expected that "moxifloxacin, like the other fluoroquinolones before it, would be toxic," and given the safe alternatives, would not have had reason to use it in a topical ophthalmic composition. Tr. 961:24-963:15 (Zhanel); *see also* Tr. 932:15-933:4; 961:24-964:1, 896:6-19 (same calculus would have dissuaded POOS from using moxifloxacin for conjunctivitis). Moxifloxacin, like most of the toxic quinolones listed in PTX 2025, had passed non-human preclinical testing and Phase I human testing in a small number of healthy volunteers. It had not passed the far more important Phase III testing in a much larger number of infected patients with higher sensitivity to toxicity. Tr. 949:18-950:24; 906:25-907:7, 961:24-964:1. As Dr. Zhanel explained, moxifloxacin's success in those early phases of testing would not have indicated to a POOS that it would be safe in actual patients. *Id.*; Tr. 899:1-24.

For this reason, Teva's reliance on the Bremm declaration as purportedly demonstrating the safety of moxifloxacin is misplaced. The Bremm declaration presented only preclinical tests, which are "poorly predictive" of human toxicity, as shown by the fact that every one of the toxic quinolones tested in patients had looked safe in preclinical tests. Tr. 899:1-900:9 (Zhanel). While Teva and Dr. Allen rely on a statement in the Bremm declaration that moxifloxacin was the best tolerated compound in the author's experience, Dr. Allen admitted that he lacks

expertise in "the area of toxicity or predicting toxicity," especially with regard to quinolones, Tr. 243:1-20, making the comfort he purports to draw from this statement of dubious relevance. Moreover, even Dr. Allen admitted that this statement would have been understood by the POOS to refer only to phototoxicity, one of the "dozens and dozens" of kinds of toxicity that would have interested a POOS. Tr. 334:19-337:5; 328:10-330:24 (Allen); 960:21-961:23 (Zhanel) (declaration's statements and data regarding tolerability have "nothing to do with human safety"). A POOS would have understood the Bremm declaration and the other published preclinical results to show that moxifloxacin—like many toxic quinolones before it—had not shown toxicity in non-human testing. The POOS would not have concluded that this meant that moxifloxacin would not be toxic in human patients. Tr. 899:1-900:9; 960:21-961:23 (Zhanel).

The same is true of the Phase I testing that Teva and Dr. Allen trumpet. "Phase 1 testing is not predictive of what will happen in the general population," because it involves subjects who are "completely different" from actual patients, including patients receiving surgical prophylaxis. Phase I subjects are young, very healthy, extensively examined, and small in number (generally less than 100)—they can "take a huge insult without displaying toxicity"; actual patients are comparatively old, unhealthy, infected, susceptible to toxicities, and numerous (millions). Tr. 900:10-904:8, 949:18-950:11 (Zhanel). As Dr. Zhanel explained, Phase I testing provides a "very preliminary assessment" of toxicity that, in the case of quinolones, is "poorly predictive of the ultimate toxicity of the compound." *Id.*; Tr. 906:25-907:7, 1144:24-1145:22, 1110:2-1111:17. Indeed, few compounds fail in Phase I, but almost all quinolones ultimately are found to be toxic. *Id.*; *see also* Tr. 901:19-902:8. Therefore, that moxifloxacin had passed Phase I testing would have done nothing to alter the POOS' expectation "that moxifloxacin, like every other quinolone that has been studied except cipro and ofloxacin, . . . will be toxic." Tr. 955:3-

956:12; 1110:2-1111:17; 948:16-949:13; 907:13-908:20; PTX 2025 (most of the listed compounds passed Phase I, all were toxic, and not one was used in an ophthalmic composition).

Indeed, the POOS in 1998 would have been aware of numerous quinolones much farther along in development than moxifloxacin that appeared non-toxic during preclinical and clinical testing but nonetheless proved unacceptably toxic. For instance, temafloxacin, trovafloxacin, and other quinolones were not toxic in preclinical and all phases of clinical tests, only to later be found to cause very serious toxicities. Tr. 907:13-914:5, 921:21-930:25 (Zhanel); PTX 209, 210, 212, 214, 215, 2025. Importantly, many of these toxicities were idiosyncratic, meaning that they were not dependent on the dose of compound circulating in the blood and could have occurred upon topical ophthalmic administration. Tr. 907:13-914:19 (Zhanel). Indeed, fatal idiosyncratic toxicity had previously been associated with topical ophthalmic administration of antibiotics, including chloramphenicol and sulfonamides. Tr. 400:11-401:19 (Alfonso), 916:19-920:23 (Zhanel); PTX 232-33. In addition, sparfloxacin, clinafloxacin, and grepafloxacin cause a potentially fatal cardiac toxicity associated with quinolones as a class that was known to occur upon ophthalmic administration and would have been a "huge issue" of concern for a POOS considering a quinolone for ophthalmic use. Tr. 934:19-947:1 (Zhanel); PTX 233. Thus, contrary to Teva's implication, the fact that lower blood concentrations result from ophthalmic administration than systemic administration would not have assuaged the POOS' concern. Tr. 908:24-911:9; 916:19-921:18; 931:18-934:7 (Zhanel); Tr. 400:11-401:19 (Alfonso). Not surprisingly, because artisans expected them to be toxic like virtually all quinolones, no ophthalmic composition containing any of the foregoing promising quinolones was pursued in trials or used in patients either before or after they displayed toxicity. Tr. 934:19-947:1; 948:16-949:17; 1138:8-19; 963:12-15 (Zhanel); 265:14-23 (Allen) (POOS would not have used a toxic

compound ophthalmically); 402:19-403:1 (Alfonso); PTX 233; PTX 2025.

Dr. Allen was not deterred by this history because he did not consider it (and lacks the expertise to comment meaningfully on it) – the only quinolones he considered were ofloxacin and cipro, the exceptions to the rule of quinolone toxicity. Tr. 270:22-271:20. And Teva's hindsight argument that a POOS would have had interest in using moxifloxacin in an ophthalmic composition is belied by this contemporaneous reality. Quinolones that had far more promising toxicity data than moxifloxacin, and would have had a more attractive risk-benefit profile than moxifloxacin, were known by 1998 and not pursued ophthalmically. Tr. 911:11-914:5, 921:21-930:25 (Zhanel); PTX 209, 210; 212; 2025. As Dr. Zhanel testified, given the risk-benefit ratio, "no-one in their right mind would have taken a quinolone" such as moxifloxacin at this stage of development and made a topical ophthalmic formulation. Tr. 1061:5-1063:6, 931:1-17.

D. Moxifloxacin Unpredictably Is a "More Effective" Ophthalmic Antibiotic

Despite the expectation that it would be unable to meet the goals and requirements in the field, topical ophthalmic moxifloxacin has achieved all of them. When applied in a topical ophthalmic composition, moxifloxacin is able to overcome its inferior activity to treat and prevent intraocular *pseudomonas* infections, including resistant strains, as effectively as cipro, without resistance developing rapidly. Tr. 423:14-426:23 (Alfonso); PTX 242-43; 892:11-893:3 (Zhanel). As discussed above, the prior art provided no reason for a POOS to believe that moxifloxacin could achieve this unpredictable result and a large body of literature indicated to a POOS that "anywhere you think *pseudomonas* is an issue, don't go there" with moxifloxacin. 1017:3-1018:22; 890:11-893:3 (Zhanel); 425:16-426:14 (Alfonso). Likewise, and surprisingly, topical ophthalmic moxifloxacin has proven to be very safe. Tr. 420:25-423:13 (Alfonso); 620:24-25 (Stroman). Given the disclosures of the prior art and the unpredictability of

quinolones as a class, the success of moxifloxacin in meeting the needs in the field was entirely unanticipated. Tr. 854:20-856:7, 892:11-893:3 (Zhanel); 420:25-426:23; 439:5-19 (Alfonso).

E. The Record Evidence Compels a Finding of Nonobviousness

Under well-established legal principles, the foregoing factual record mandates a finding that claim 1 is not obvious, for multiple reasons.

The Supreme Court in *KSR* clarified that in assessing obviousness, courts should look to the contemporaneous realities in the field of the invention. Courts should consider whether the "problem known in the field," "demands . . . in the marketplace", "trends" in the field, "background knowledge possessed by" the POOS, and the explicit prior art disclosures would have given the POOS a reason to arrive at the claimed invention, with a reasonable expectation of success. *KSR*, 127 S. Ct. at 1740-42. Here, the contemporaneous realities compel the rejection of Teva's obviousness contentions. Because of the known problems with existing therapies discussed above, there was a demand for, and skilled workers in the field were trying to find, a composition that was more effective than, and as safe as, Ciloxan® and Ocuflox® in treating and preventing intraocular infections caused by both *pseudomonas* and *staph*. Moxifloxacin would not have been viewed as meeting these needs. Section I.C. Further, the trends in the field, given toxicity issues and the emergence of quinolone resistance, were moving away from quinolones, which were not even "on the radar screen in terms of looking for an appropriate antibacterial" for ophthalmic use. Tr. 419:11-420:2; Section I.C.3-5. That was especially true for quinolones like moxifloxacin that the prior art showed had significantly reduced activity against *pseudomonas*, the most feared ocular pathogen. Section I.C.2-5. The contemporaneous realities did anything but suggest the obviousness of the claimed invention.

It is axiomatic that if the prior art as a whole would not have led a POOS to believe that an invention would solve the problem in the field, the invention cannot be obvious. *See, e.g.*,

Takeda, 492 F.3d at 1362 (invention not obvious where POOS would not have expected it to overcome toxicity problem). Teva does not attempt to show that a POOS would have expected ophthalmic moxifloxacin to solve the problems facing the field in September 1998. Rather, Teva asserts that a POOS would have reasonably expected that a moxifloxacin composition would be "an antibacterial composition" or a composition with "antibacterial properties." Teva Br. at 33-35. That misses the point. There was no demand or need for a composition merely possessing "antibacterial properties," nor is there any evidence that a POOS would have had reason to make such a composition absent a belief that it would solve the actual problems in the field. Teva's argument is thus entirely divorced from the contemporaneous realities that guide the obviousness inquiry and wholly inadequate to prove obviousness. *See United States v. Adams*, 383 U.S. 39, 52 (1966) (invention not obvious because a POOS would have believed it was "not practical").

Most fundamentally, Teva's decision to ignore the issue of whether a POOS would have selected moxifloxacin to solve the problems in the field is fatal to its obviousness defense. Both before and after *KSR*, courts assiduously have analyzed whether a POOS would have started with a given compound in assessing whether an invention is obvious in view of a reference disclosing that compound. *See, e.g., Ortho-McNeil*, 520 F.3d at 1364-65 (POOS "would not even be likely to start with" compound on which obviousness theory relied, precluding finding of obviousness); *Takeda*, 492 F.3d at 1360, 1362 (no obviousness absent proof that the "prior art would have led to the selection of compound b" as starting point); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378-79 (Fed. Cir. 2006) (invention not obvious where "the state of the art would have directed the [POOS] away from" using the compound on which defendant relied).[6]

[6] *See also Yamanouchi Pharm. Co., Ltd. v. Danbury Pharm., Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (finding invention nonobvious because the Defendant "did not show the required motivation for selecting" the compound on which it relied amongst all the compounds in the art);

Teva offered no evidence that a POOS would have selected moxifloxacin for ophthalmic use. As one court aptly stated in granting summary judgment of nonobviousness on the basis of the very flaw that mandates rejection of Teva's defense here, the defendant "has skipped over the first step [involving selection of compounds for treatment of diabetes] and begun its theories with the second [how to formulate them]. This is starting, if not midstream, then at least ankle-deep." *Ortho-McNeil Pharm., Inc. v. Mylan Labs. Inc.*, 2007 WL 432792, at *5-6 (D. N.J. Feb. 5, 2007).

By ignoring the question of whether a POOS would have selected moxifloxacin, Teva and Dr. Allen ignored the art that taught away from that selection. Section I.C. It is black letter law that all prior art, including art that "teaches away," must be considered in assessing whether a claimed invention is obvious. *Adams,* 383 U.S. at 51-52; *In re Sullivan,* 498 F.3d 1345, 1351-53 (Fed. Cir. 2007); *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999); *In re Legator*, 352 F.2d 377, 380 (C.C.P.A. 1965) ("all properties of [compound] must be considered in light of all the requirements for a suitable agent [for the claimed use] when considering the question of obviousness of the claimed invention"). A reference "teaches away" when "a [POOS], upon reading the reference, . . . would be led in a direction divergent from the path that was taken by" the inventor. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The art discussed above, which repeatedly indicated moxifloxacin's inferiority against *pseudomonas* and suggested that its use would exacerbate rather than solve the major problem of *pseudomonas* resistance, was ignored entirely by Dr. Allen. Tr. 277:4-280:19. And the unrebutted evidence was that the art as a whole taught away from using moxifloxacin in the eye, where *pseudomonas* is an important pathogen. Section I.C.2-4. Of course, if the prior art collectively teaches away from the claimed invention, it cannot be obvious. *See, e.g., Takeda*, 492 F.3d at 1360, 1362.

Bayer AG v. Dr. Reddy's Labs., Ltd., 518 F. Supp. 2d 617, 625-28 (D. Del. 2007); *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 536 F. Supp. 2d 476, 495 (D. Del. 2008).

For all of these reasons, Teva's obviousness defense fails.

1. Teva Improperly Relies on the Inventors' Actions in Its Attempt to Prove Obviousness

Because it cannot prevail under a proper obviousness analysis, Teva advances arguments that courts repeatedly have rejected as a matter of law. First, Teva relies heavily on the inventors' own writings, actions, and work to contend that their invention was obvious. That is impermissible – "the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." *Life Techs., Inc. v. Clontech Lab., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000). Indeed, section 103 expressly provides that "[p]atentability shall not be negatived by the manner in which the invention was made," which renders immaterial whether the invention resulted from a "long toil and experimentation or from a flash of genius." 35 U.S.C. § 103 Revision Notes and Legislative Reports, 1952 Notes.[7]

In direct contravention of this authority, Dr. Allen squarely admitted that his "opinion that Alcon's claim is obvious is based in part on the fact that the Alcon inventors chose to focus on moxifloxacin for topical ophthalmic use." Tr. 354:14-17 (Allen). Instead of retreating from Dr. Allen's impermissible approach, Teva fully embraces it and then compounds the error by mischaracterizing the inventors' legally irrelevant work. Teva Br. at 7-8, 10-13, 35-36.

Teva suggests that the Alcon inventors decided to develop a moxifloxacin ophthalmic product based on information available in the prior art, incorrectly implying that if this were true,

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[7] *See also CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1340 (Fed. Cir. 2003) ("patent acquisition does not require any threshold level of effort or ingenuity"); *Shiley, Inc. v. Bentley Labs., Inc.*, 794 F.2d 1561, 1568 (Fed. Cir. 1986) (though inventor "immediately conceived the successful design to obtain a known result" upon viewing prior art, "patentability of an invention does not depend on how the invention was made"); *Purdue Pharma LP v. Endo Pharms., Inc.*, 438 F.3d 1123, 1132 (Fed. Cir. 2006) ("a patent application for a pharmaceutical discovery" need not be supported by "clinical results" as "the manner in which an invention is discovered, whether by insight or experiment, does not by itself affect patentability").

the invention must have been obvious. Not only is this legally baseless, but Teva egregiously mischaracterizes and oversimplifies the process that Alcon used. While Teva is correct that Dr. Stroman learned of the compound moxifloxacin from seeing a Bayer poster, that has nothing to do with the issue at hand. Seeing such a poster at a conference was hardly a unique experience for Dr. Stroman. Rather, throughout the 1990's, Alcon was looking for a new topical ophthalmic antibiotic that was "better than the two state-of-the-art products" in treating and preventing intraocular infections and as safe as these products. Tr. 566:6-570:6 (Stroman). In attempting to find a suitable compound, Dr. Stroman did not choose among "five or six" possibilities as Teva suggests. Teva Br. at 36. Dr. Stroman obtained five or six compounds from a single conference, which he selected from the hundreds if not thousands of abstracts presented, and similarly identified compounds at numerous other conferences throughout the 1990's. Tr. 572:10-573:6 (Stroman); 339:15-344:25 (Allen). The universe of possibilities was thus the innumerable quinolone and non-quinolone antibacterials that had been published in the literature. Tr. 72:7-73:23 (Taylor) (hundreds of publications disclosing new quinolones); 898:15-25 (Zhanel). And from among these thousands of options, Dr. Stroman (not the prior art) selected several hundred that he wished to screen, most of which were not quinolones, in order to determine whether they met Alcon's criteria. Tr. 570:7-571:1; 641:2-24 (Stroman).[8] Before moxifloxacin, not one did. Teva's invocation of *KSR*'s discussion of choosing amongst a finite number of *identified, predictable* solutions is thus wholly inapt, both because the solutions were not identified by the prior art and the solution of using moxifloxacin was anything but predictable. Section I.C, I.D.

[8] Dr. Stroman testified that he screened "a hundred" compounds and identified another "two or three" hundred that "I never got into the lab." Tr. 570:7-19. The transcript omits the word "hundred" from Dr. Stroman's estimate of the number of compounds he requested but did not receive, but the context—including his testimony about five to ten compounds he sought and did not receive from one conference alone—shows that this was a transcription error. Tr. 572:10-17. Alcon has submitted an errata today to correct this error and the error addressed in footnote 13.

Before he tested moxifloxacin, Dr. Stroman viewed it essentially as no different from the other hundred compounds he had previously screened without success, and did not believe that Alcon would pursue it ophthalmically. Tr. 585:21-587:2. On the contrary, Dr. Stroman requested a sample of moxifloxacin to screen, despite his "concern" regarding its inferior *pseudomonas* activity, because the corporate relationship between Bayer and Alcon made it likely he could gain access to Bayer's compound and non-public toxicity information—considerations that certainly would not have impacted a POOS (and show the fallacy of relying on inventors' actions when examining what the POOS would have done). Tr. 571:2-572:17; 609:11-610:22. Ultimately, ophthalmic moxifloxacin displayed properties that met Alcon's criteria, including the "very surprising" equivalence to cipro in treating intraocular *pseudomonas* infections. Tr. 592:10-598:12; 610:23-615:2; PTX 361, 363. Alcon would not have pursued ophthalmic moxifloxacin had it not obtained these surprising results; it certainly would not have done so based on information publicly known in 1998. Tr. 595:20-23; 614:17-615:2.[9]

In a related error, Teva repeatedly relies on the fact that Alcon's testing of ophthalmic moxifloxacin compositions began after the priority date. Conflating the distinct concepts of innovation and performing experiments, Teva interprets this sequence of events as proof that the invention of the '830 patent is "not innovative." Teva Br. at 7, 26, 34-36. That is wrong as a matter of both fact and law. How an inventor came up with an idea, whether while sitting under

[9] Ignoring the law rendering them irrelevant to obviousness and the unrebutted testimony about them that refutes its arguments, Teva repeatedly relies on documents written by Dr. Stroman's coinventors about the development of ophthalmic moxifloxacin. Contrary to Teva's suggestion, Alcon's development decision resulted from the surprising test results it obtained, not some corporate strategy of following oral dosage forms into the market, the expiry of the cipro patent (which would provide no reason to select moxifloxacin), or moxifloxacin's publicly known properties. *See* Tr. 592:10-598:12; 610:23-615:2, PTX 361; PTX 363-E, H (showing that Alcon decided to pursue moxifloxacin only after its testing surprisingly showed superior ocular pharmacokinetics and ability to treat intraocular *pseudomonas* infections); Tr. 666:21-676:10 (Stroman) (explaining DTX 68 and 69); 643:3-645:13 (Stroman) (explaining DTX 64).

an apple tree or after years of painstaking experimentation, is irrelevant to patentability. A "patent application for a pharmaceutical discovery" need not be supported by "clinical results" as "the manner in which an invention is discovered, whether by insight or experiment, does not by itself affect patentability." *Purdue*, 438 F.3d at 1132 (emphasis added). Indeed, whether an inventor had proven experimentally that his idea was worthwhile has no bearing on whether he conceived an inventive idea. *See In re Jolley*, 308 F.3d 1317, 1325 (Fed. Cir. 2002).

Not content with its legally erroneous position, Teva mercilessly twists the record to assert that Alcon's experts and inventor somehow agreed that the "'830 patent is not innovative." Teva Br. at 34-36. But the testimony, cited by Teva selectively, shows just the opposite. Tr. 466:6-468:2; 553:22-554:18 (Alfonso) (while POOS would not have thought the inventors' idea was worthwhile in 1998, in fact, that idea was a "major breakthrough" in the field); Tr. 1017:3-1018:22; 1024:7-1025:15; 1061:5-1063:6; 931:1-17; 876:12-879:20; 980:14-984:4) (Zhanel) (the invention was so innovative that it ran directly contrary to numerous trends in the field and teachings in the art). Nor does Dr. Stroman's testimony that he did not believe that ophthalmic moxifloxacin would meet Alcon's criteria when he filed his application "disclaim[] any inventive activity in connection with the '830 patent," unless one adopts Teva's legally and factually impermissible equation of experimental proof with conception of a novel and innovative idea.[10]

2. *Daiichi* Does Not Help Teva

Teva asks this Court to conclude, despite the overwhelming evidence to the contrary, that claim 1 is obvious because in a different case, with a different record, the Federal Circuit found a different invention obvious. Teva Br. at 22, 26 (citing *Daiichi*, 501 F.3d at 1258). The Federal

[10] Dr. Mitra's testimony that the patent does not contain anything "innovative as far as the drug delivery system is concerned," is exactly correct and confirms that the invention is directed to the choice of moxifloxacin as an active ingredient. Tr. 769:20-770:11. Dr. Mitra plainly did not testify that there is nothing innovative in the patent, as Teva misleadingly suggests. Br. at 35.

Circuit has consistently rejected the notion that a court may do so, as an obviousness inquiry is based on underlying factual findings in a given case. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007) ("Courts cannot decide the obviousness or non-obviousness of a patent claim by proxy. [Doing so] certainly invites error as decisions on obviousness must be narrowly tailored to the facts of each individual case."); *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992) ("Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts."); *In re Ochiai*, 71 F.3d 1565, 1571 (Fed. Cir. 1995) ("Section 103 requires a fact-intensive comparison of the claimed [invention] with the prior art").

The factual records in *Daiichi* and this case are very different. The Federal Circuit in *Daiichi* expressly premised its holding that the prior art's disclosure of cipro for the treatment of ear infections rendered obvious the claimed invention of using ofloxacin to treat ear infections on the undisputed expert testimony that the art indicated that "Ofloxacin would be very likely equally as effective as Ciprofloxacin when used topically to treat middle ear infections." 501 F.3d at 1258. Far from being "very similar to the facts of" *Daiichi*, Teva Br. at 22, no one testified here that a POOS would have expected moxifloxacin to be equally as effective as cipro in treating and preventing intraocular infections, let alone that it would meet the requirements for a new ophthalmic antibiotic. *See, e.g.*, Tr. 897:6-21; 1017:3-1018:22; 854:26-856:7, 892:11-893:3; 981:2-984:1 (Zhanel); 420:25-426:23 (Alfonso). Rather, the undisputed record shows that a POOS would have expected moxifloxacin to be "likely less effective" than cipro, drive *pseudomonas* resistance, be less safe than cipro, and be wholly unsuitable for ophthalmic use. *Id. Daiichi* does not remotely suggest that an invention is obvious on such a record.[11]

[11] To the extent that any record mirrors the record here, *Legator*, 352 F.2d at 379-80, presented a situation where microbiological data indicated that an antibiotic may be useful to treat infections

The record is devoid of any evidence that Alcon's invention is obvious; Teva's only witness ignored the relevant issues and lacks the expertise to address them. In stark contrast, Alcon's evidence of non-obviousness is overwhelming.

F. Objective Indicia Confirm the Nonobviousness of Claim 1

1. The Claimed Invention Was Greeted with Skepticism, Met a Long-Felt Need, and Achieved Commercial Success

Objective indicia of non-obviousness, such as skepticism in the field, long-felt need, and commercial success, must be considered in an obviousness determination, *Graham*, 383 U.S. at 17-18; *In re Johnston*, 435 F.3d 1381, 1385 (Fed. Cir. 2006). The evidence was undisputed that upon hearing that Alcon intended to pursue an ophthalmic composition containing moxifloxacin, actual artisans in the field were more than skeptical—they were "upset" and downright "dismay[ed] that we were wasting so many resources in looking at yet another quinolone that was the source of the problems that we were facing in 1998," because the prior art suggested that moxifloxacin was unsuitable for ophthalmic use. Tr. 415:2-416:10; 420:19-24; 487:14-490:17 (Alfonso). That an idea was greeted with such skepticism is powerful evidence that it was not obvious without the benefit of hindsight. *Adams*, 383 U.S. at 52 (patent non-obvious because "at the time Adams perfected his invention noted experts expressed disbelief in it"); *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 697-98 (Fed. Cir. 1983) ("Expressions of disbelief by experts constitute strong evidence of nonobviousness."). It was likewise undisputed that ophthalmic moxifloxacin met the long-felt and critical need for a composition that could more effectively treat intraocular infections caused by all important ocular pathogens, without resistance developing. *See* Section I.D. Finally, Teva stipulated that Vigamox®, an embodiment

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"of the respiratory tract," but unworthy of selection for the different claimed use, "in light of all the requirements for a suitable agent." The court found the "selection invention" patentable. *Id.*

of the claim, has achieved hundreds of millions of dollars in sales, D.I. 75, ¶4, and the evidence showed that this commercial success resulted from the properties of the invention—safety and efficacy. Tr. 420:25-423:13 (Alfonso); 621:1-11 (Stroman). *See Johnston*, 435 F.3d at 1385.

2. The Invention Exhibits Unexpected Pharmacokinetic Properties

Because "that which would have been surprising to a [POOS] in a particular art would not have been obvious," unexpected properties of an invention refute a contention that it was obvious, regardless of whether those properties were known at the time of the invention or discovered later. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995); *Sullivan*, 498 F.3d at 1352-53; *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1384-85 (Fed. Cir. 2004).

a. A POOS Would Not Have Expected the Invention's Superior Ocular Pharmacokinetics

Moxifloxacin compositions can treat and prevent intraocular infections caused by all key pathogens, despite inferior *pseudomonas* activity, due to their ocular pharmacokinetic properties that are superior to the ciprofloxacin and ofloxacin compositions of the prior art and that permit high concentrations to penetrate and remain in the infected tissues. Tr. 892:11-893:3 (Zhanel); 420:25-423:13 (Alfonso). As Teva's expert admitted, and Alcon's experts explained, topical ophthalmic moxifloxacin compositions, throughout the range of .1-1%, display desirable ocular pharmacokinetics that "would not have been predicted by anything in the prior art prior to 1998" and that permit effective treatment and prevention of intraocular infections. Tr. 364:8-366:9; 358:23-360:15 (Allen); 715:4-7; 722:12-723:10; 718:4-16 (Mitra); 854:1-856:7 (Zhanel).

The eye has a multi-layered anatomical framework designed to keep foreign compounds out. As a result, most compounds do not penetrate and remain in the eye in high concentrations. Tr. 697:4-705:18; 718:17-723:10; 817:23-818:12 (Mitra); 376:6-385:24 (Alfonso); 854:6-855:19 (Zhanel); PTX 2030A-C, E-I. As Dr. Mitra testified, in 1998, "there was no data" published

regarding the ocular pharmacokinetic properties of moxifloxacin, and a scientist could not have predicted the ocular pharmacokinetic properties of compositions containing moxifloxacin. Tr. 715:4-6; 722:12-723:10 (Mitra); 419:2-10 (Alfonso); 854:6-856:7 (Zhanel).[12]

Teva tries to change the subject to the irrelevant question of whether moxifloxacin would have been expected to penetrate the eye at all. Teva Br. at 35. But the question is whether ophthalmic compositions of moxifloxacin would penetrate far better than the prior art cipro and ofloxacin compositions; that they do so, and accordingly meet the requirements in the field, was entirely unexpected. Tr. 802:19-803:7 (Mitra); PTX 363, 386, 1116; Section I.D.; *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 969 (Fed. Cir. 2006) (claimed skin unclogging method non-obvious, due to unexpectedly high blackhead removal ratio of 23% compared to 4% in prior art).

Teva contends that Dr. Mitra "conceded that a [POOS] would have expected in 1998 that moxifloxacin would . . . more readily penetrate the eye than ofloxacin." Teva Br. at 20-21. He did not. He testified that ocular pharmacokinetics depend on, among other factors, passive diffusion through the cornea, which in turn depends on lipophilicity and weight. Tr. 706:12-707:21. He explained that penetration cannot be predicted based only on lipophilicity, "because there are so many other parameters" besides lipophilicity that cannot be ignored. Tr. 707:9-710:6. Nevertheless, holding all other factors equal, he stated that an artisan would conclude that moxifloxacin would penetrate "at a slightly lower rate and amount than ofloxacin." Tr. 710:7-711:5. Dr. Mitra clarified again (783:20-784:5) and again (786:14-20) and again (802:12-18) that the lipophilicity data alone suggested lower penetration for moxifloxacin than ofloxacin.[13]

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[12] The solubility data in PTX 1098 on which Teva relies (at 20) is not pharmacokinetic data, does not reflect its relevant solubility at the neutral pH in the eye's tear film, and does not predict the ocular pharmacokinetics of ophthalmic moxifloxacin compositions. Tr. 707:9-710:6 (Mitra).

[13] Ignoring this testimony—including its own counsel's apology for wrongly suggesting that Dr. Mitra testified that moxifloxacin formulations would have been expected to penetrate better than

Teva's argument has a more fundamental flaw. Lipophilicity is only one factor of many that impact a compound's penetration and retention upon topical administration. There is no evidence that, when all factors are considered, a POOS would have expected moxifloxacin to penetrate and remain in ocular tissues in high concentrations. On the contrary: (1) its molecular weight suggested it would penetrate less than cipro and ofloxacin; (2) the extent of moxifloxacin's penetration by active transport could not have been predicted; (3) there was no data to suggest that moxifloxacin could avoid being effluxed out of the eye; and (4) a POOS could not have predicted that moxifloxacin could avoid drug loss from aqueous humor turnover by binding to the iris-ciliary bodies. Tr. 711:9-715:7, 718:22-723:6 (Mitra). There was no basis for a POOS to expect that moxifloxacin compositions would exhibit superior ocular pharmacokinetic properties to the cipro and ofloxacin compositions of the prior art. *Id.*

Teva's unsupported statement that the ocular pharmacokinetics of moxifloxacin "had been disclosed in the prior art," Teva Br. at 32, is thus refuted conclusively by the evidence.[14]

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ofloxacin formulations, Tr. 783:20-784:5—Teva relies on a clear error in the transcript to suggest that Dr. Mitra testified that moxifloxacin would be expected to penetrate better. Teva Br. at 21 (citing Tr. 786:21-787:18) (moxifloxacin "will be much better than ofloxacin")). In fact, in another part of the very answer on which Teva relies, Dr. Mitra states that moxifloxacin would be expected "to be no better than ofloxacin at all." And Teva's counsel did not interpret Dr. Mitra to be saying that moxifloxacin would be expected to penetrate better than ofloxacin (as Teva now argues), as he rejoined "But one would predict that it will penetrate." Tr. 787:16.

[14] Grasping at straws, Teva tries to extract a disclosure of moxifloxacin's ability to penetrate the eye from articles disclosing its penetration into "extravascular tissues" and "cerebrospinal fluid" ("CSF") upon systemic administration. Teva Br. at 20 (citing PTX 223, DTX 191). The undisputed evidence was that these articles have nothing to do with penetration into the eye upon topical administration. "Extravascular" refers to penetration from the blood to various tissues (not including the eye); the POOS would "absolutely not" understand the reference to "extravascular tissue" in PTX 223 to pertain to ocular penetration. Tr. 952:1-17 (Zhanel); 515:24-516:3; 548:17-550:21 (Alfonso). Likewise unsupported is Teva's syllogism that because moxifloxacin penetrated into CSF upon systemic administration, and because the brain and the eye are the two most protected organs, moxifloxacin would have been expected to penetrate the eye upon topical administration. Teva Br. at 20 (citing DTX 191). The evidence was unrebutted that the eye and brain, while both protected, are protected in entirely different ways, and

b. Topical Ophthalmic Moxifloxacin Compositions Display Unexpected Pharmacokinetic Properties Superior to Ofloxacin and Cipro Compositions Throughout the Scope of the Claim

Dr. Mitra analyzed data generated at Alcon using the well-accepted "Schoenwald" model demonstrating that moxifloxacin compositions penetrate the cornea to a far greater extent than compositions containing cipro and ofloxacin. Tr. 604:3-24; 724:23-730:13; PTX 1116, 312. Unpredictably, the data – which are applicable to the context of topical administration to human eyes, Tr. 790:11-791:21; 807:19-810:10 – showed that the amount of moxifloxacin that penetrates the cornea is about seven times higher than cipro and two-and-a-half times higher than ofloxacin—a "very significant difference" that (as explained above) was not predictable. Tr. 724:23-730:13; 743:12-744:8; PTX 1116. These data were consistent with Alcon's in vivo testing, which showed that moxifloxacin unpredictably penetrated into intraocular tissues in higher concentrations than other quinolones upon ophthalmic administration, including ofloxacin (which was known to penetrate better than cipro). Tr. 596:6-603:10 (Stroman); PTX 363-H; 383 at AL002-000645; 386 (moxifloxacin concentrations higher than ofloxacin in the aqueous humor, cornea, iris-ciliary body, and vitreous humor by factors of more than 3, 2.5, 3.5, and 4.5).

These pharmacokinetic properties hold the key to the success of ophthalmic moxifloxacin and explain the successful treatment of intraocular *pseudomonas* infections that the art suggested it would be unable to cover. Tr. 892:11-893:3 (Zhanel); 420:25-423:13 (Alfonso). Because moxifloxacin compositions penetrate and are retained in significantly greater concentrations than compositions containing ofloxacin and cipro, more moxifloxacin is available for a longer period of time to treat and prevent infections in intraocular tissues. *Id.*; Tr. 730:14-731:9 (Mitra). In addition, this greater retention of moxifloxacin unpredictably permits more effective prevention

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penetration into CSF has nothing to do with ocular pharmacokinetics upon topical ophthalmic administration. Tr. 519:15-520:5; 550:9-552:1 (Alfonso); 957:18-958:1 (Zhanel).

of the Lasik-related mycobacterium infections that were a grave concern of artisans in 1998. Tr. 420:25-431:10 (Alfonso); 850:16-852:19 (Zhanel); PTX 228-29, 386.

Moxifloxacin compositions possess these surprising pharmacokinetic properties throughout the claimed concentration range of .1 to 1%. It is undisputed that moxifloxacin compositions are far superior to cipro and ofloxacin compositions at low concentrations. PTX 1116, 363, 386; Tr. 723:16-743:22 (Mitra). Because the moxifloxacin compositions' penetration over the .1-1% range is linear (which is the best a composition can achieve), the relative pharmacokinetic superiority of moxifloxacin compositions is—at the very least—retained throughout the scope of the claim. *Id.*; PTX 1119, 2021; Tr. 604:3-606:17 (Stroman). Even Dr. Allen did not disagree that moxifloxacin compositions throughout the range of .1-1% have a greater ability to penetrate the eye than therapies existing in 1998. Tr. 365:16-366:9.

Finally, Dr. Mitra explained (and Teva did not dispute) that basic ocular pharmacokinetic principles dictate that moxifloxacin compositions' superior penetration extends to all compositions of claim 1.[15] *See In re Kollman*, 595 F.2d 48, 56 (C.C.P.A. 1979) (unexpected properties of "a broader claimed range can, in certain instances, be proven by a narrower range of data. Often, one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof."); *E.I. Du Pont de Nemours & Co. v. Phillips Petrol. Co.*, 656 F. Supp. 1343, 1368 (D. Del. 1987). This is true irrespective of the vehicle used and irrespective of whether the composition is a solution, suspension, ointment, or gel. Tr. 820:8-822:11; 704:25-705:18 (Mitra); PTX 2030-C.[16]

[15] Dr. Mitra thus had no need to test every embodiment of the claim in comparison to cipro and ofloxacin. Such an analysis is both infeasible and entirely unnecessary, as the law recognizes.

[16] The extent of passive diffusion across the cornea depends on (1) the concentration of compound in the tear film, and (2) the proportion of the drug in the tear film that penetrates the cornea. Tr. 820:8-822:11; 776:23-783:9; 704:25-705:18 (Mitra). The particular vehicle in which

c. The Court Should Not Exclude Dr. Mitra's Testimony or PTXs 364, 365, 366, and 1116

Unable to refute Dr. Mitra's testimony, Teva attempts to make it disappear by lodging a spurious evidentiary attack on both his testimony and four exhibits, PTXs 364-66 and 1116. Teva Br. at 2-4. At trial, Teva did not object to PTX 366 and there is no basis for it to do so now.[17] Tr. 607:2-6. As to the remainder, in essence, Teva contends that Dr. Mitra changed his opinion at trial and that Teva did not have an opportunity to depose Dr. Mitra regarding the subject of his trial testimony. Both of Teva's allegations are flatly contradicted by the record.

At trial, Dr. Mitra opined that "moxifloxacin ophthalmic compositions exhibit superior pharmacokinetic properties over the compositions of the other two quinolones, ciprofloxacin and ofloxacin, over the entire range of concentrations in the Claim 1." Tr. 723:21-724:9. This is the identical opinion Dr. Mitra's disclosed in his expert report: "the claimed moxifloxacin formulation has superior ocular pharmacokinetics than the topical ophthalmic formulations of ofloxacin and ciprofloxacin . . . across the entire range of moxifloxacin concentrations (.1% to

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the compound is administered will impact the first factor; once dissolved in the tear film, the compound will behave the same way independent of the vehicle. *Id.* Thus, the vehicle will impact the compound's concentration in various ocular tissues, but the "advantage of moxifloxacin composition[s] will prevail" with "[a]ny kind of solution, any ointment, gel, suspension." *Id.*; Tr. 743:12-744:1; 732:5-734:21; 779:25-783:9; PTX 1116. That the vehicle plays no role after the drug dissolves in the tear film does not mean that pharmacokinetics are a property of the drug, rather than the entire composition. Tr. 816:11-817:4; 823:19-824:2 (Mitra). All pharmacokinetic properties result from the composition as a whole; the drug cannot be administered by itself. Tr. 695:17-696:19; 511:23-512:16 (Alfonso). It is only moxifloxacin in a topical ophthalmic composition—the claimed invention—that possesses unexpected pharmacokinetic properties, not moxifloxacin itself. Tr. 816:11-817:4; 823:19-824:2 (Mitra).

[17] The exhibits and testimony to which Teva did not object show that the claimed moxifloxacin compositions are unexpectedly superior to compositions containing ofloxacin and cipro. PTX 363, 386; Tr. 596:6-606:17. PTX 366, to which Teva did not object, shows that this superiority is conserved throughout the scope of claim 1. Tr. 603:18-606:17; 736:23-743:11; PTX 1119, 2021. Thus, the record shows that the claimed invention displays unexpected properties, regardless of whether Dr. Mitra's testimony and the other exhibits are excluded.

1.0%) recited in claim 1 of the '830 patent." Ex. A (Responsive Expert Report of Ashim K. Mitra, Ph.D.) ¶ 18. The notion that Dr. Mitra changed his opinion before trial is specious.

The suggestion that Teva did not have a fair opportunity to depose Dr. Mitra is likewise meritless. This entire controversy is a tempest in teapot. Teva seeks to use a mistaken deposition answer having no bearing on the substance of Dr. Mitra's opinion as a pretext to exclude his testimony. Dr. Mitra mistakenly testified at his deposition that to generate the data he reviewed in PTX 1116, the various compounds' commercially optimized formulations were used (as was true for other data Dr. Mitra reviewed in PTX 386). Tr. 747:6-750:21; 770:12-771:25. Using the commercial compositions of compounds is a recognized way to control for the vehicles used in the tested compositions. Because scientists presume that the commercial compositions have optimized the compositions' pharmacokinetic properties, artisans compare commercial compositions "all the time," even though the vehicles are different. Tr. 817:5-22; 818:13-22 (Mitra); PTX 1117, 386. In fact, the commercial compositions were not used in PTX 1116; rather, the same vehicle was used for all the compositions, the other recognized way to control for the vehicle. Tr. 731:10-732:4 (Mitra). Despite Teva's suggestion to the contrary, this error had no effect whatsoever on Dr. Mitra's opinions. It makes no difference which of the techniques is used; either way, one is controlling for the vehicle. Nor do the particular contents of the vehicle make a difference in this comparative analysis. Tr. 810:11-17; 731:10-733:7.[18]

After Teva raised this issue at his deposition, Dr. Mitra investigated further by reviewing the underlying lab notebooks and learned that identical vehicles were used. Tr. 810:18-815:13.

[18] For this reason, and contrary to Teva's suggestion that Dr. Mitra's analysis in this case differed from his usual practice, Dr. Mitra does not generally review the underlying laboratory notebooks when he reviews Schoenwald data. The testimony Teva cites (Teva Br. at 4) relates to Dr. Mitra's practices when "doing the experiment" in his own lab, as compared to instances where (as in this case) he "did not go do the experiment [and] prepare the solutions." Tr. 762:19-764:4.

Alcon promptly provided these lab notebooks (which did not alter Dr. Mitra's opinions) to Teva, advised Teva that Dr. Mitra may rely on them at trial, and invited Teva's counsel to contact Alcon's to discuss the matter. Ex. B. Despite Alcon's letter, Teva neither asked for additional information from Alcon nor requested to re-depose Dr. Mitra. In fact, Teva did nothing at all, waiting until trial months later to object to Dr. Mitra's testimony and the notebooks. Teva was on more than fair notice about Dr. Mitra's trial testimony, and any theoretical prejudice from Dr. Mitra's mistaken answer months before trial could have been easily cured had Teva raised an issue in a timely manner.[19] The Court should deny Teva's request to exclude his testimony and PTXs 364-66 and 1116. *See In re Paoli*, 35 F.3d 717, 791 (3d Cir. 1994); Tr. 811:4-814:14.

II. THE '942 PATENT DOES NOT ANTICIPATE CLAIM 1 OF THE '830 PATENT

Anticipation requires that a single prior art reference place a POOS in possession of the claimed invention, by disclosing every claim limitation arranged as in the claim. *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1338 (Fed. Cir. 2008); *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). As Teva's brief all but acknowledges, and the record shows, the '942 patent does not disclose every limitation of claim 1, certainly does not disclose them arranged as in the claim, and does not place a POOS in possession of Alcon's invention.

A. The '942 Patent Does Not Disclose Every Limitation of Claim 1

Claim 1 requires a topical ophthalmic composition comprising moxifloxacin in a concentration of .1 to 1.% and a pharmaceutically acceptable vehicle. PTX 5. The '942 patent describes neither the concentration range of .1-1% (or a concentration within that range) nor a "pharmaceutically acceptable vehicle" and thus cannot anticipate.

[19] Far from requiring Teva to "unearth the basis of the expert's opinions by plowing through [a volume of] data without further guidance," these small notebooks repeatedly show the vehicle used. *E.g.*, PTX 364 at 6, 12, 19; PTX 365 at 8, 14. If Teva wanted "guidance," it could have contacted counsel for Alcon or re-deposed Dr. Mitra. Instead, Teva buried its head in the sand.

With regard to the range, the '942 patent provides that the billion compounds it discloses "should preferably be present . . . in a concentration of about .1 to 99.5, preferably about .5 to 95% by weight of the total mixture." PTX 3, Col. 56, ll. 7-11. Controlling law dictates that these extremely broad ranges do not describe the claimed range of .1-1%.

In *Atofina*, 441 F.3d at 999, the Federal Circuit addressed whether the prior art's disclosure of overlapping and encompassing temperature ranges of 150-350 and 100-500 degrees disclosed the claimed range of 330-450 degrees. The defendant, like Teva here, argued that the prior art's disclosure of a range discloses species both within and at the endpoints of the range, and that those species "fall within" and thus anticipate the claimed range. *Id.*; Teva Br. at 37-39 (citing *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781 (Fed. Cir. 1985). The Federal Circuit rejected that argument, holding that the "disclosure is only that of a range, not a specific temperature in that range" and that in view of the "considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this limitation of the claim." *Atofina*, 441 F.3d at 999-1000. The differences between the ranges in the '942 patent (.1-99.5% and .5-95%) and claim 1 (.1-1%) are manifestly more "considerable" than the differences that the *Atofina* court held non-anticipatory as a matter of law. *See also* Tr. 976:8-977:15 (Zhanel).

Atofina ends the anticipation inquiry here, as Teva's futile efforts to distinguish the case reveal. Teva argues that, in view of the active ingredient concentrations in Ciloxan® and Ocuflox® – which are referenced nowhere in the '942 patent – a POOS would interpret the '942 patent to disclose concentrations of .35% and .3%. Teva Br. at 38-39. Teva's effort to combine the '942 patent with other prior art is a transparent obviousness argument, which requires a distinct analysis of whether the prior art as a whole would have provided a reason to substitute

moxifloxacin into Ciloxan® or Ocuflox®. *Torpharm, Inc. v. Ranbaxy Pharms., Inc.*, 336 F.3d 1322, 1326 n.3 (Fed. Cir. 2003) ("[N]ovelty and nonobviousness are separate concepts that are best kept analytically distinct."); *Duro-Last, Inc. v. Custom Seal, Inc.*, 321 F.3d 1098, 1107 (Fed. Cir. 2003). Dr. Allen's testimony cannot make concentrations of .3% and .35% magically appear in the '942 patent, nor can it make the differences between the ranges of the patent and claim 1 any less "considerable." Tr. 306:7-307:2 (Allen); 976:5-977:15 (Zhanel); *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) (rejecting argument that "missing elements may be supplied by the knowledge of [POOS] or the disclosure of another reference").[20] Moreover, it is wrong. Tr. 976:8-977:15 (Zhanel). Even more desperate is Teva's contention (at 39) that the '942 patent inherently discloses a range of .1-.5% (a range of the endpoints of the disclosed ranges), which not only lacks any factual support but also conflicts directly with *Atofina's* holding that the "disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points." *Atofina*, 441 F.3d at 1000.

The '942 patent also does not describe the "pharmaceutically acceptable vehicle" of claim 1. While Dr. Allen referred to the '942 patent's disclosure of water in connection with this element, as Dr. Mitra explained, water alone is not a pharmaceutically acceptable vehicle, a point that neither Teva nor Dr. Allen refuted. Tr. 192:15-193:5 (Allen); Tr. 695:23-696:10 (Mitra). Nor can Teva rely on the '942 patent's listing of excipients other than water. The '942 patent provides no disclosure at all regarding which of its excipients are suitable for ophthalmic use and may be combined to form a pharmaceutically acceptable vehicle in an ophthalmic composition,

[20] *See also Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (anticipation does not allow POOS to "complete the work required for the invention"); *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 485-86 (D. Del. 2006) (POOS "cannot supply missing elements through his or her knowledge"); *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) ("finding of anticipation . . . is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations").

which even Dr. Allen agrees must be sterile, non-irritating, non-toxic, and maintain the stability of the active ingredient. Tr. 275:13-277:3; 309:15-311:20 (Allen); 977:16-978:9 (Zhanel). Nor did Dr. Allen identify which of the excipients together constitute a pharmaceutically acceptable ophthalmic vehicle. Thus, for this independent reason, the '942 patent cannot anticipate claim 1.

B. The '942 Patent Does Not Disclose the Invention of Claim 1 to a POOS

Teva's anticipation argument relies on the '942 patent's disclosure of moxifloxacin as one of more than a billion compounds and the general disclosures (wholly unconnected to moxifloxacin) that the compounds may be used in a broad dosage range (.1-99.5%) in dozens of formulations (one of which is ophthalmic) to treat approximately one hundred diseases (one of which is eye infections). The disclosures on which Teva relies are unconnected in the '942 patent; they appear together only in a chart prepared by Dr. Allen (who was testifying regarding the meaning of the '942 patent to a formulator, not to the POOS). DTX 4011. Teva's approach fundamentally misunderstands the anticipation inquiry, which concerns whether a prior art reference places a POOS in possession of the invention, not whether a reference's unconnected snippets may be re-arranged to recite the claim limitations in a different manner than the reference discloses them. *Finisar*, 523 F.3d at 1338; *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1384 (Fed. Cir. 2006) (Rader, J., concurring); *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 496 F. Supp. 2d 428, 431 (D. Del. 2007).

The '942 patent nowhere discloses to a POOS the invention of a topical ophthalmic composition containing .1-1% moxifloxacin and a pharmaceutically acceptable vehicle. Tr. 975:5-977:15 (Zhanel); 302:18-308:22 (Allen). As even Dr. Allen agreed, all of the statements upon which Teva relies in the '942 patent regarding concentration ranges, compositions, and diseases refer to the over a billion compounds of the invention generally, not moxifloxacin

specifically. Tr. 299:12-300:17 (Allen); 973:21-975:4; 967:18-968:11; 969:20-970:14 (Zhanel); 80:7-11 (Taylor). Teva's argument is contrary how a POOS would understand the '942 patent.

A POOS would understand the statements on which Teva relies "to be general and potentially say that there may be a compound [among the over a billion] that could treat one or more of these infections." Tr. 968:2-975:4 (Zhanel). A POOS would not read the disclosure of the '942 patent, as Teva and Dr. Allen do, to indicate that all billion-plus compounds, or any particular one of them, can be used in each of the dozens of compositions to treat each of the approximately one hundred listed diseases. Tr. 295:8-296:8; 299:12-300:17; 285:22-291:9 (Allen); 974:25-975:4 (Zhanel). That interpretation strains credulity; no compound in history has been able to treat every disease listed in the patent; the POOS would not interpret it to disclose that the inventors have discovered not one, but a billion, compounds that do so. Tr. 969:20-970:14 (Zhanel); 294:21-295:3 (Allen).

Given the broad, general statements in the '942 patent regarding the potential uses, concentrations, and compositions of the compounds of the invention, a POOS would look to other information in the patent to determine whether it discloses a specific compound in a specific composition in a specific dosage range. Tr. 970:15-971:17 (Zhanel). The '942 patent does not disclose any data for moxifloxacin, any data for *pseudomonas*, or any data regarding ocular infections, and its preferred concentration range of .5-95% includes virtually everything except the .3% concentration at which topical ophthalmic compositions generally are used. *Id.* These disclosures (or lack thereof) all indicate to a POOS that a topical ophthalmic composition containing moxifloxacin was not disclosed amongst the billions of potential compound-composition combinations. *Id.*; 976:5-977:15 (Zhanel). And lest any doubt remain, the '942 patent does not disclose any formulation containing moxifloxacin (in contrast to the compound

of Example 1, Col. 53), does not disclose any ophthalmic formulation at all, and does not disclose any formulation within the range of .1-1% of any compound—much less a moxifloxacin ophthalmic composition within that range. Tr. 975:5-976:8 (Zhanel).

Dr. Allen tries to justify applying general statements regarding more than a billion compounds to moxifloxacin in particular on the bases that the '942 patent "mentions moxifloxacin as the preferable drug," "pull[s] out moxifloxacin" as "being the preferred example in the patent," and suggests that it had been synthesized, tested, and confirmed to be appropriate for ophthalmic use. Tr. 176:13-178:12; 264:23-266:14; 180:11-20. To the contrary, the '942 patent discloses more than one million compounds other than moxifloxacin as "particularly preferred" and does not so designate moxifloxacin; provides synthetic information about more than 50 exemplified compounds, but not moxifloxacin; and provides microbiological data for approximately 20 compounds, once again not including moxifloxacin. Tr. 968:12-969:11; 970:15-973:2 (Zhanel). Thus, a POOS would have concluded that moxifloxacin had not even been synthesized, let alone tested, when the specification was written—a conclusion that the evidence confirms. Tr. 972:1-973:20 (Zhanel); PTX 262.[21] Dr. Allen's hindsight effort to assert that the '942 patent discloses a topical, ophthalmic moxifloxacin composition is plainly wrong.

The Federal Circuit recently confirmed that Teva's approach of mixing and matching disclosures of a prior art reference to prove anticipation is improper. In *Finisar*, 523 F.3d at 1338, the defendant relied on a chart (similar to Dr. Allen's DTX 4011, Tr. 186:2-193:5) that mapped the claim limitations to "various pages of" the allegedly anticipatory reference. Noting

[21] While moxifloxacin is claimed in the '942 patent, a POOS—a scientist, not a patent attorney—would not understand the significance of that compound being claimed and would instead look to the data to ascertain compounds' properties. Tr. 971:18-25 (Zhanel). There certainly is no reason, other than litigation-inspired hindsight, that a POOS would conclude that the '942 patent claimed moxifloxacin because it was suitable for (of all things) ophthalmic use.

the requirement that "an anticipatory reference must disclose not only each limitation of the claim, but also each of those limitations arranged as in the claim," the court held that the correlation of disparate disclosures from a reference to the claim elements insufficient to prove anticipation. *Id.*; *see also Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1480 (Fed. Cir. 1986). The same principle applies here: the '942 patent no more discloses to a POOS a topical ophthalmic formulation containing moxifloxacin in the claimed dosage range than the Home Depot catalog discloses a particular Cape Cod house that may be constructed from disparate materials listed in the catalog. Thus, even if all of the claim limitations were separately disclosed (and they are not), the '942 patent cannot anticipate claim 1 of the '830 patent.

III. TEVA'S BEST MODE DEFENSE IS MERITLESS

Ignoring the actual record in the case, and relying on and mischaracterizing inadmissible testimony from a different case that is not part of the trial record, Teva argues that the '830 patent is invalid for violation of the best mode requirement. A best mode violation requires clear and convincing evidence (1) that the inventor had a best mode of practicing the invention "that he considered to be better than any other," and (2) that the best mode was not disclosed in sufficient detail to allow a POOS to practice it without undue experimentation. *Chemcast Corp. v. Arco Indus.*, 913 F.2d 923, 926-28 (Fed. Cir. 1990). Neither of these requirements is met here.

A. The Use of BAY 12-8039 Was Not Dr. Stroman's Best Mode

Teva asserts that Dr. Stroman's best mode of practicing the invention at the priority date was to use BAY 12-8039 (moxifloxacin hydrochloride) to make the claimed composition, and that the patent's disclosure of "moxifloxacin" rather than "moxifloxacin hydrochloride" or "BAY 12-8039" concealed his best mode. Teva Br. at 40-43. Teva can only make this argument by studiously ignoring the trial record. Dr. Stroman's best mode of practicing the invention of a

topical ophthalmic composition containing moxifloxacin was to use a solution containing moxifloxacin. Tr. 577:18-578:19 (Stroman). The '830 patent discloses a solution containing moxifloxacin, thus precluding violation of the best mode requirement. PTX 5 at Col. 6, ll. 35-47.

Contrary to Teva's suggestion, the use of the compound having Bayer's numerical designation "BAY 12-8039" instead of moxifloxacin was not Dr. Stroman's best mode of practicing the invention. When he learned of BAY 12-8039, Dr. Stroman associated the number with the active compound (later called moxifloxacin), not any particular salt form of it (like moxifloxacin hydrochloride ("HCl")). Tr. 642:4-23. Dr. Stroman could not possibly have had a preference for BAY 12-8039 instead of moxifloxacin: he thought they were one in the same. Indeed, Dr. Stroman testified that "I can't say that I ever even understood there was [a] salt form because I was focused on the active" compound, moxifloxacin. Tr. 577:18-578:19. That he would not be interested in the salt form is not surprising. Dr. Stroman was interested in making a solution. The evidence was undisputed that as a matter of basic scientific principle, salt forms of a compound do not exist in a solution – once the compound dissolves, the salt breaks away and all that is left is the active molecule. Tr. 93:10-95:5, 96:11-97:3 (Taylor); 577:18-578:19 (Stroman); PTX 2031B. Thus, whether it was prepared using moxifloxacin or moxifloxacin HCl or some other salt form, the preferred solution would be the same. Tr. 93:10-97:3 (Taylor).

The contemporaneous record confirms Dr. Stroman's testimony that he understood the compound BAY 12-8039 to be simply moxifloxacin.[22] Tr. 580:4-582:3; PTX 402 at 1 (agreement signed days after the priority date indicating that Alcon wanted "moxifloxacin," without any salt form identified); 582:11-583:20, PTX 399 (letter to Bayer soon after priority

[22] Moreover, there are repeated references in the literature to BAY 12-8039 as moxifloxacin, without mention of any salt form. PTX 135, 137; DTX 170, 195. Even Teva itself does so, citing Dr. Alfonso's testimony that moxifloxacin was a known antibiotic for the proposition that "moxifloxacin HCl was known to possess antibacterial properties." Teva Br. at 32.

date requesting "moxifloxacin," without identifying any particular salt); 584:3-25; PTX 89 (form filled out by Dr. Stroman upon receipt of 10 grams of material, equating "moxifloxacin" with BAY 12-8039).[23] There is no evidence whatsoever that at the priority date (when he had not yet even received any compound from Bayer), Dr. Stroman considered BAY 12-8039 "to be better than" moxifloxacin, and overwhelming evidence that he did not, as he considered them to be one and the same. *Chemcast*, 913 F.2d at 928; Tr. 646:15-647:4; 654:6-655:12; 577:18-578:19.[24]

Teva attempts to eliminate the requirement that Dr. Stroman had a subjective preference for the allegedly concealed mode by contending that Dr. Stroman only knew of BAY 12-8039 (which happens to be the HCl salt form) and thus, pursuant to the Federal Circuit's decision in *Chemcast*, 913 F.2d at 928, was required to disclose it. Teva Br. at 41. *Chemcast* does nothing to help Teva, as it explicitly acknowledges, and expressly does not abrogate, the requirement that an inventor must possess a subjective preference for a particular best mode in order to violate the best mode requirement. *Id.* at 927-28. In *Chemcast*, the inventor used a material manufactured specifically for him and that he knew had the particular hardness he preferred for practicing the invention. *Id.* at 929. Though the inventor possessed only one material for practicing the invention, he had a preference for that material over all others and believed it possessed properties that were important in practicing the invention. *Id.* In stark contrast to *Chemcast*, there is not a shred of evidence to suggest that Dr. Stroman considered the use of BAY 12-8039 "to be better than" moxifloxacin. *Id.* He thought they were the same and did not even realize as

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[23] Though the compound request form processed by Alcon's licensing department shows the structure of moxifloxacin HCl, Dr. Stroman did not draw that structure or believe that the compound he was requesting was a specific salt form. PTX 1065, Tr. 578:20-580:1 (Stroman).

[24] Thus, even assuming Teva were correct that the law required Dr. Stroman to disclose in the patent the form of moxifloxacin he knew of, he did so. Dr. Stroman understood BAY 12-8039 to be "moxifloxacin," not any particular salt form. And he disclosed moxifloxacin in the patent.

of the priority date that BAY 12-8039 was a salt form, let alone consider the salt form relevant.

Teva's claim fails for an independent reason. As a matter of law, an inventor need not disclose ingredients used to make a composition unless they have a "material effect on the properties of the claimed invention." *Bayer AG v. Schein Pharms., Inc.*, 301 F.3d 1306, 1321 (Fed. Cir. 2002). The record is undisputed that the use of moxifloxacin (also called the betaine) instead of moxifloxacin HCl to make a solution does not have a material effect on the claimed solution. Tr. 96:11-97:3 (use of a different salt will not impact solution, and use of moxifloxacin instead of moxifloxacin HCl will make "no difference whatsoever"); 93:10-95:22 (Taylor); 771:25-776:10; 818:21-820:7; 1031:11-1033:13; 1119:9-1120:3 (Zhanel); PTX 262, PTX 264.[25]

Finding no record evidence that the use of moxifloxacin HCl instead of moxifloxacin has a "material effect on the properties of the claimed invention," Teva cites out of context a snippet of testimony from Bayer scientist Dr. Uwe Petersen from the trial of a different case to which Alcon was not even a party. This testimony, which is plainly inadmissible hearsay, is not part of the trial record of this case and Teva's citation of it should be stricken. Indeed, Teva never even tried to make it part of the trial record, nor did it seek permission to re-open the record to include it. That is clearly improper. It is astonishing that Teva would even cite this testimony given this Court's post-trial order denying Teva permission to re-open the trial record to introduce Dr. Petersen's deposition testimony from this case. Ex. C (March 14, 2008 Order). And the fact that Dr. Petersen had planned to testify by live video from Germany in this case in part to address this

[25] Dr. Taylor's testimony that Teva cites indicates that some HCl salts may be more soluble, but does not demonstrate that the choice of salt will impact the composition itself, which is what the law requires. Teva Br. at 43. Because moxifloxacin and moxifloxacin HCl are both soluble through the entire scope of the claim, the only difference in the compositions made by these forms would be the pH, which easily can be buffered to make them identical. Tr. 93:10-95:21 (Taylor); PTX 2031A,B; 818:21-820:7 (Mitra); 678:7-685:1 (Alford). The effect of the salt form on the moxifloxacin composition is thus at most negligible, not "material" as the law requires.

very issue, and both parties agreed that such testimony was unnecessary after the Bayer settlement, makes Teva's citation to testimony from the prior case all the more improper.

In any event, contrary to Teva's suggestion, there is no difference between an ophthalmic solution using moxifloxacin HCl and moxifloxacin betaine as starting materials. Dr. Zhanel "looked at all the data [and] can tell you, concretely, that there is absolutely no difference between the betaine and the hydrochloride in terms of their microbiological activity. . . There is no difference in the toxicity. And there can't be. Once the drug is fully in solution, it is moxifloxacin that impacts" the properties, including toxicity. Tr. 1036:21-1038:4. And Bayer contemporaneously treated the salt forms of moxifloxacin interchangeably, and the reason it developed the HCl salt rather than the betaine, contrary to Teva's theory, related to practicality of handling, not toxicological properties. Tr. 1040:8-1041:4; 1119:9-1129:19; PTX 94-97.

B. Even if the Use of BAY 12-8039 Had Been His Best Mode, Dr. Stroman's Disclosure of Moxifloxacin Satisfied the Best Mode Requirement

Unlike *Chemcast*, where the public was not aware of the particular material the inventor used and concealed, BAY 12-8039 was the "moxifloxacin" that was known in the art. As the literature reflects, a POOS would have understood the patent's disclosure of a "moxifloxacin" composition to be synonymous with a BAY 12-8039 composition. *See* PTX 135, 137; DTX 170, 195 (referring to "moxifloxacin" as BAY 12-8039). The law is clear: if a POOS would know the best mode, there can be no violation. *High Concrete Structures, Inc. v. New Enter. Stone & Lime Co.*, 377 F.3d 1379, 1382-83 (Fed. Cir. 2004) (best mode "not violated by unintentional omission of information that would be readily known to persons in the field of the invention").[26] And, in

[26] *See also Young Dental Mfg. Co. v. Q3 Special Prods*, 112 F.3d 1137, 1145 (Fed. Cir. 1997) ("[A]n inventor need only disclose information about the best mode that would not have been apparent to one of ordinary skill in the art."); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58 (Fed. Cir. 1983) (disclosure analyzed based on "knowledge extant in the art");

fact, because Dr. Stroman's preferred solution is the same irrespective of whether it was prepared using moxifloxacin or moxifloxacin HCl, the moxifloxacin solution he disclosed is identical to the moxifloxacin HCl solution that Teva contends was his best mode. Tr. 93:10-97:3 (Taylor).

IV. TEVA'S ENABLEMENT DEFENSE IS WHOLLY UNSUPPORTED

Teva also contends that claim 1 is not enabled, which requires clear and convincing evidence that the patent does not enable a POOS to practice the claimed invention without undue experimentation. *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993). Teva has no evidence to support this argument. Accordingly, Teva tries to reverse the burden of proof to contend that Alcon failed to prove that its claim is enabled. The law requires no such showing, and Teva's absence of evidence necessarily precludes a finding of non-enablement. *Id.*

No witness testified that claim 1 is not enabled. Rather, every witness testifying on the subject agreed that making the claimed compositions, with the '830 patent in hand, is a trivial task. As Dr. Alfonso explained, it "wouldn't be difficult" for a POOS, with the patent, to make the claimed compositions; in fact, someone with much less training and experience could do so. Tr. 554:23-556:8; 412:15-415:1. He also testified that it would be "routine" and "easy" to modify the procedures and make compositions throughout the claim's scope. Tr. 447:6-450:24; 452:2-455:7; 554:23-556:8.[27] And far from offering opinions "not based on any relevant work or experience," he explained that ophthalmic compositions are prepared "in my laboratory," and that ophthalmologists receive training in making formulations and "prepare a number of

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McNeil-PPC, Inc. v. Perrigo Co., 516 F. Supp. 2d 238, 257-58 (S.D.N.Y. 2007) ("[T]here can be no best mode violation where a person of ordinary skill would have known the purported best mode through the scientific literature."); *Ajinomoto Co. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1346 (Fed. Cir. 2000) (disclosure in literature satisfied best mode requirement).

[27] Teva suggests that because the procedure Dr. Alfonso outlined differed from that employed by Ms. Alford, his procedure would not work. Teva Br. at 48. There is no evidence to support any such conclusion, as multiple procedures may work to produce the claimed formulations.

formulations extemporaneously," as he himself has done. Tr. 411:1-415:1; 454:19-21.[28]

Dr. Zhanel testified that microbiologists likewise learn how to prepare formulations as part of their training and do so routinely. Tr. 991:14-993:22; 837:11-838:7. He explained that "a microbiologist, given a recipe, for example, in the '830 patent, could easily make an ophthalmic composition," and that his graduate students (below the level of a POOS) could prepare the claimed compositions. Tr. 992:11-993:22; 1002:18-1004:20. Dr. Zhanel then explained how he would prepare various compositions of claim 1, demonstrating that even without explicit recitation of "process steps," a POOS easily could prepare the claimed compositions, whether they be solutions, suspensions, ointments, or otherwise.[29] Tr. 994:19-1004:20.

Teva seeks to discount Dr. Zhanel's unrebutted testimony that he and his students could prepare the claimed formulations by contending that those formulations "are not suitable for administration to patients" and thus not within the scope of claim 1. Teva Br. at 48, 31, 26. That is nonsense. The issue is not whether microbiologists often make pharmaceutical compositions, but rather whether they could do so. Dr. Zhanel explained that microbiologists "would be the first to know how to make an ophthalmic formulation, given a recipe that would be potentially pharmaceutically acceptable." Tr. 992:11-993:22; 1002:18-1004:6 (POOS "would not have a problem . . . making a pharmaceutically acceptable formulation"; "it's not difficult"). That the

[28] Teva seizes on Dr. Alfonso's testimony that "others in his laboratory" make the formulations, without citing his testimony that those individuals have "high school degrees" and "an associate degree," far less education and training than either side's POOS. Br. at 48; Tr. 414:8-415:1.

[29] Dr. Zhanel's testimony that he has "put together ophthalmic ointments" and discussion of how a POOS would prepare a suspension of claim 1 conclusively refute Teva's argument that "there was clearly no testimony that supports the conclusion that the [POOS] as defined by Alcon's experts would be able to formulate a proper gel, suspension, ointment or any other type of composition" of claim 1. Teva Br. at 50. Tr. 994:19-1004:6. And Dr. Alfonso's testimony that ophthalmologists can and do prepare ophthalmic formulations for their patients was in no way limited to solutions. Tr. 411:1-415:1; 454:19-21. In any event, the issue is not whether the testimony "supports" enablement, but rather the absence of evidence to prove non-enablement.

formulations microbiologists prepare on a daily basis do "not necessarily . . . have to be pharmaceutically acceptable because we are not necessarily using these preparations for humans," Tr. 996:15-997:9, is utterly beside the point. And contrary to Teva's repeated assertions that Dr. Zhanel's formulations "should certainly never be allowed to be placed in the eyes," Teva Br. at 26, 48-49, Dr. Zhanel responded to Teva's question of whether his "compositions [are] suitable to administer to the eye," by stating, "I have made compositions to be suitable for the eye. Do I make them frequently? Absolutely not." Tr. 992:10-25; 848:6-7. Teva simply ignores this testimony and urges the Court to make a contrary, unsupported finding that a POOS with training in microbiology cannot make compositions suitable for the eye.[30]

If there were any doubt that a POOS could prepare the claimed compositions with minimal experimentation, it was resolved by the testimony of Ms. Kathleen Alford. Ms. Alford, a microbiologist with a master's degree and no specialized experience making ophthalmic formulations, was directed to prepare certain compositions of the '830 patent using only the patent's disclosure. Tr. 677:3-685:4. She prepared five compositions within the scope of claim 1 in about four hours, including a lunch break. *Id.*; PTX 86. Teva has no response to this testimony, other than to point out that Ms. Alford, who was able to prepare the claimed compositions without any experimentation, has less training than Alcon's POOS, which of course militates in favor of a finding of enablement. Teva Br. at 49.[31]

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[30] Teva argues that Dr. Zhanel admitted that "he would not allow" a hypothetical composition made by his student into his eye. Teva's question assumed that this composition had not been shown to be nontoxic and made no mention it being nonirritating, both prerequisites to a composition being pharmaceutically acceptable. Tr. 1002:18-1004:14; Teva Br. at 26, 31, 48-49. It is thus not surprising that Dr. Zhanel was unwilling to participate in an *ad hoc* test of such a composition to "see whether it's toxic." *Id.*

[31] Teva also contends that because she did not test the osmolality of her compositions, they may not have been pharmaceutically acceptable. Teva Br. at 49. Teva confuses the burden of proof – Teva presented no evidence that the formulations were not pharmaceutically acceptable.

Finally, Teva ignores the fact every expert agreed that the POOS would have expertise and experience in formulation, and it is undisputed that the claim is enabled if the POOS has this qualification.[32] Tr. 412:7-9 (Alfonso); 232:17-234:6 (Allen). The evidence was uniform: a POOS, or even a person with considerably less training could prepare the compositions of claim 1 with virtually no experimentation. There is no contrary evidence. The absence of "process steps," Teva Br. 47, is thus legally and factually irrelevant. A specification need not "explain every detail" since the patent "is speaking to those skilled in the art." *DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985). Teva's argument that a patent is not enabled because it did not disclose the process of preparing the compositions, when all witnesses agreed it was exceedingly simple to do, would turn "patent specifications . . . into production specifications, which they were never intended to be." *Id.; Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006).

V. THE '830 PATENT FULLY DESCRIBES THE CLAIMED INVENTION

Finally, Teva contends that claim 1 is invalid because the specification does not indicate that the inventors were in possession of the claimed invention. Teva Br. at 43-44. In particular, Teva argues that (1) the specification indicates that the inventive compositions must contain a separate preservative, (2) claim 1 does not require this "essential element" and thus (3) claim 1 includes subject matter (compositions without a preservative) not described by the specification. Teva Br. at 43-44 (citing *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1480 (Fed. Cir. 1998)). The Federal Circuit has explicitly repudiated Teva's "essential element" theory that the description of an invention as including a particular element (a preservative) requires that the claim explicitly include that element. *See Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc.*, 291 F.3d 1317, 1322-23 (Fed. Cir. 2002). That alone is sufficient to reject Teva's defense.

[32] The dispute as to the definition of the POOS is not whether the POOS possesses these skills, but whether this is the only skill possessed. *See* Section I.B.1.

Aside from its legal infirmity, Teva's written description argument is based on an erroneous factual premise: that the specification requires, and thus only describes compositions containing, a separate preservative.[33] Teva Br. at 44. In fact, Example 3 in the specification specifically describes a composition without a separate preservative. Tr. 1006:3-1007:7 (Zhanel); 438:11-439:1; 556:9-557:6 (Alfonso). Teva has no answer to this disclosure. It therefore asks the Court to simply ignore Example 3 – and then conclude that the patent has an inadequate written description because the very thing it is ignoring is absent. Teva Br. at 45.[34] There simply is no basis for the Court to ignore Example 3 as Teva suggests.

Moreover, the language in the specification Teva relies on discloses that ophthalmic "products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use." PTX 5 at Col. 5:66-6:1. As Dr. Alfonso explained, and a POOS would have understood, this language provides that the compositions of the invention may be packaged in multidose or single dose containers – the latter not needing a separate preservative. Tr. 435:3-438:10; 456:24-457:9 (Alfonso); 311:21-312:12 (Allen). There is thus no dispute that the specification discloses in two separate places compositions that need not contain a preservative, and Teva's argument therefore fails. *Id.*

CONCLUSION

For the foregoing reasons, Teva's invalidity defenses should be rejected.

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[33] Teva's argument also relies on the premise that claim 1 includes compositions without a preservative. Teva Br. at 44. To the contrary, moxifloxacin itself acts as a preservative and is present in all compositions of the claim. Teva's premise is thus wrong. 437:21-438:10; 456:24-457:9; 556:9-557:6 (Alfonso); 1006:3-1007:7 (Zhanel). Teva's argument therefore fails for this additional reason.

[34] In support of this argument, Teva cites *Sinorgchem Co. v. ITC*, 511 F.3d 1132, 1138 (Fed. Cir. 2007), which addresses the entirely distinct question of whether a claim may be construed to exclude an embodiment. Here, the question is whether the specification (which includes Example 3) describes the invention of claim 1, which indisputably covers Example 3.

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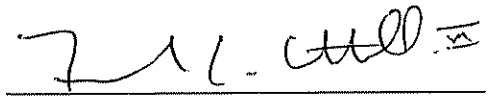

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CERTIFICATE OF SERVICE

I hereby certify that on July 2, 2008, I caused to be served by hand delivery the foregoing document and electronically filed the same with the Clerk of Court using CM/ECF which will send notification of such filing(s) to the following:

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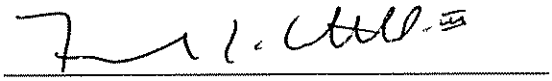

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EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER HEALTHCARE AG, ALCON, INC., and ALCON MANUFACTURING, LTD., Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 06-234 (SLR) **HIGHLY CONFIDENTIAL – OUTSIDE ATTORNEYS' EYES ONLY**

RESPONSIVE EXPERT REPORT OF ASHIM K. MITRA, Ph.D.

I. Background

1. I am the Curators' Professor of Pharmacy and Chairman of the Division of Pharmaceutical Sciences at the University of Missouri in Kansas City. I am also Vice Provost for Interdisciplinary Research at the University of Missouri, and Director for Translational Research at the University of Missouri School of Medicine. Prior to joining the University of Missouri in 1994 as a full Professor, I was an Associate Professor of Physical Pharmacy at Purdue, and before that, an Assistant Professor at Purdue and the University of Nebraska Medical Center.

2. My expertise is in the area of drug delivery and disposition, and in particular, ocular drug delivery and disposition. I received a Ph.D. degree from University of Kansas in 1983 in Pharmaceutical Chemistry. My thesis was entitled "Passive and facilitated transport of pilocarpine across the corneal membrane of the rabbit." I have over 25 years of experience in ocular penetration, drug delivery, and disposition. My CV is attached as Exhibit 1A.

3. As Director for Translational Research at the School of Medicine, I am involved in selecting new technologies from bench research, particularly in the ophthalmic area, and

coordinating preclinical studies for the purpose of filing an investigational new drug application with the U.S. Food and Drug Administration. As Chairman of the Division of Pharmaceutical Sciences, my responsibilities include hiring new faculty members, evaluating their performances on a yearly basis, recommending faculty for tenure and promotion, supervising all the graduate students and the staff in the division, reporting to the dean and serving on the executive committee of the School of Pharmacy.

4. I have authored and co-authored over 200 refereed articles, published in, among other journals, International Journal of Pharmacology, International Journal of Pharmaceutics, Investigative Ophthalmology & Visual Science, Molecular Vision, Current Eye Research, The Journal of Ocular Pharmacology and Therapeutics, Pharmaceutical Research, European Journal of Pharmacology, Journal of Pharmacy and Pharmacology, Journal of Pharmaceutical Sciences, Current Drug Metabolism, Molecular Pharmaceutics, Journal of Controlled Release, Life Sciences, Expert Opinion on Drug Delivery, AAPS Pharm Sci Tech Journal, Drug Delivery, American Journal of Therapeutics, Molecular and Cellular Biochemistry, Letters in Drug Design and Discovery, European Journal of Pharmaceutics and Biopharmaceutics, Clinical Research in Regulatory Affairs and Drug Development, and Industrial Pharmacy. My work has also been presented at several universities, pharmaceutical companies and scientific organizations worldwide, the most notable being the International Conference on Ocular Diseases and Their Treatment (Germany 1997), XVI International Congress of Eye Research Conference (Australia 2004), BioMedical Transporters 2005 Conference (Switzerland 2005), Ophthalmic Drug Development and Delivery Summit (San Diego 2007), China International Drug Delivery Systems Summit 2005 (China 2005), and the Annual Meetings of the Association for Research in Vision and Ophthalmology, and the American Association of Pharmaceutical Scientists.

5. I have served as Editor of the 1993 and 2003 editions of the well-known text book, Ophthalmic Drug Delivery Systems. I have authored or co-authored over twenty chapters for various texts relating to ocular drug delivery. Some of these chapters describe, among other things, the effects of physicochemical properties of drug substances and their permeation across various corneal tissues and their pharmacokinetics in ocular fluids and tissues.

6. I serve on the editorial advisory board for Bentham Science Publishers, International Journal of Pharmaceutics, AAPA Pharm Sci, Clinical Research and Regulatory Affairs, Current Eye Research, Current Pharmaceutical Design, and Current Drug Metabolism. I also been elected to several offices and/or served as a member of various committees of the American Association of Pharmaceutical Scientists, Association for Research in Vision and Ophthalmology, and the Controlled Release Society.

7. I actively teach numerous subjects across the pharmaceutical sciences, including drug absorption, drug transport, bioavailability and bioequivalence, and drug delivery. I have, at times, taught all of the aforementioned topics with a focus on ocular drugs. I have advised over seventy graduate students, post-doctoral fellows, resident physicians, and visiting professors and scholars.

8. Over the course of my career, I have received numerous awards and honors, including the 2007 ARVO/Pfizer Ophthalmics Translational Research Award, the University of Missouri Curators' Professor of Pharmacy Award, the American Association of Pharmaceutical Scientists Fellow Award, the UKC Trustees Faculty Research Award, and National Collegiate Inventor of the Year Award.

9. I am an inventor of two U.S. patents in the field of drug delivery, with one patent focused on ocular drug delivery.

10. My recent research activities have focused primarily on three areas (1) Ocular Disposition, Metabolism and Delivery of Antiviral Agents, (2) Nasal and Pulmonary Delivery of Macromolecules, i.e., Proteins and Antisense Oligonucleotides, and (3) Oral Absorption of Novel anti-HIV Agents.

11. I have provided expert testimony in the last four years in the following cases:

- *Allergan v. Apotex* (Ketorolac)
- *Aventis v. Apotex* (Diltiazem)
- *Novartis v. Apotex* (Calcitonin)
- *Novartis v. Apotex* (Cyclosporin)
- *GlaxoSmithkline v. Pharmascience* (Val-acyclovir).

12. I have been retained by Williams & Connolly LLP as an expert in this litigation. I am being compensated at a rate of $500 per hour. My compensation does not depend on the outcome of this litigation. If asked, I will be prepared to present a basic tutorial to explain the pharmaceutical terms and concepts used in my expert report, and anticipated during the trial. That tutorial may include demonstrative exhibits and models. In addition to the opinions and bases set forth in this report, my testimony may include responses to facts, arguments, allegations, or references raised by Teva or its experts relating to this litigation.

13. I have relied on the materials cited in this report, as well as my training and experience, in forming my opinions.

II. Person of Ordinary Skill in the Art

14. I have been asked to provide an opinion as to the qualifications of the person of ordinary skill in the art to whom the invention disclosed and claimed in Alcon's U.S. Patent No. 6,716,830 ("the '830 patent", Ex. 1B) is directed, as of September 30, 1998. Among other

things, the person of ordinary skill in the art to whom the '830 patent is directed would have knowledge regarding the treatment and prevention of ophthalmic bacterial infections by topical administration. While there are several aspects to this knowledge, as it pertains to my area of expertise and my opinions in this case, a person of ordinary skill in the art would be familiar with principles of ocular pharmacokinetics and delivery. I understand that other experts will address other aspects of the background of a person of ordinary skill.

III. Opinions

A. Summary of Opinions

15. I have reviewed the relevant literature publicly available as of September 30, 1998 (the "priority date")[1] related to the ocular pharmacokinetics of fluoroquinolones, the physiochemical properties of moxifloxacin and other fluoroquinolones, and the other factors impacting ocular pharmacokinetics, *e.g.*, tear-protein binding, carrier-mediated absorption, carrier-mediated efflux, and melanin-binding. Based on my review of the prior art, it is my opinion that one of ordinary skill in the art would not have expected the topical ophthalmic formulation of moxifloxacin recited in claim 1 of the '830 patent (the "claimed moxifloxacin formulation") to exhibit ocular pharmacokinetic properties far superior to the ophthalmic formulations of ofloxacin or ciprofloxacin available as of September 30, 1998.

16. Rather, if anything, the prior art would have taught a person of ordinary skill in the art that the claimed moxifloxacin formulation would exhibit ocular pharmacokinetic properties which are about the same as, or slightly inferior to, a topical ophthalmic formulation

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[1] I have been told by Alcon's attorneys that Teva does not dispute that the '830 patent is entitled to a priority date of September 30, 1998. I also understand from Alcon's attorneys that properties of the claimed moxifloxacin formulation discovered or reported after September 30, 1998 are relevant to the obviousness inquiry.

of ofloxacin, and which are, at most, only better than the properties of a topical ophthalmic formulation of ciprofloxacin to the extent that the prior art formulation of ofloxacin was better.

17. I have reviewed published and unpublished data related to the ocular pharmacokinetics of the claimed moxifloxacin formulation in comparison to topical ophthalmic formulations of ofloxacin and ciprofloxacin. In my opinion, the claimed moxifloxacin formulation exhibits several beneficial properties that are far superior to those of the topical ophthalmic formulations of ofloxacin and ciprofloxacin which a person of ordinary skill in the art would not have expected as of September 30, 1998.

18. The claimed moxifloxacin formulation has superior ocular pharmacokinetics than the topical ophthalmic formulations of ofloxacin and ciprofloxacin that were commercially available as of September 30, 1998. The moxifloxacin topically applied in the claimed formulation has these properties across the entire range of moxifloxacin concentrations (0.1% to 1.0%) recited in claim 1 of the '830 patent.

B. Ocular Pharmacokinetics

19. I have been instructed to assume that the reader has a familiarity with the anatomical structure of the eye given the background provided in the report of Dr. Eduardo C. Alfonso. *See* Report of Dr. Eduardo C. Alfonso ¶¶ 26-29. I agree with Dr. Alfonso's discussion of the ocular anatomy and incorporate it herein. A person of ordinary skill in the art would have been familiar with the anatomy of the eye as described in Dr. Alfonso's report.

20. The ocular pharmacokinetics of a formulation are, in part, a characterization of the extent to which the active compound (*i.e.*, the active ingredient) penetrates the corneal layers, accumulates, and, importantly, remains at the various sites in the eye where infections form and spread. A number of factors impact the ocular pharmacokinetics of a formulation, including (a)

precorneal factors like tear-protein binding to the active ingredient; (b) the extent of passive transport through the corneal layers (which, in turn, depends on at least the lipophilicity, hydrophilicity, and molecular weight of the active ingredient), (c) any active absorption of the active ingredient through the cornea (such as by a carrier system), and (d) the rate of diffusion and efflux out of the relevant ocular tissues and away from these sites of action (which in turn depends on a variety of factors, including lipophilicity, hydrophilicity, and melanin binding within the iris and ciliary bodies).

21. Prior to studying its pharmacokinetics, a person of ordinary skill in the art would not have known which factors will be significant for a particular formulation and how the factors will interact with one another and impact a formulation's ocular pharmacokinetics.

22. As of September 30, 1998, as far as I am aware, there were no reported studies on the ocular pharmacokinetics of any topical ophthalmic formulation of moxifloxacin.

23. Considering what was known at the time about how the factors mentioned above affect the pharmacokinetics of other fluoroquinolones, a person of ordinary skill in the art would not have formed a reasonable expectation that a topical ophthalmic formulation of moxifloxacin would penetrate into and achieve higher concentrations in ocular tissues far better than previously available topical ophthalmic formulations of ofloxacin and ciprofloxacin.

24. In the absence of the only information that could have provided a reasonable expectation as to a formulation's ocular pharmacokinetic properties—actual pharmacokinetic data relating to the concentrations of the active compound in relevant ocular tissues over time—a person of ordinary skill in the art might look to other information to hypothesize about what the pharmacokinetic properties of the particular formulation possibly could be. Needless to say, this exercise is fraught with uncertainty, due to the facts that a formulation's pharmacokinetic

properties depend on a variety of factors that are not themselves predictable and that these factors interact in unpredictable ways. In order to achieve the goal of attaining high tissue concentrations of active compound in (among other relevant tissues) the cornea and aqueous humor, a compound must travel to the corneal epithelium before being eliminated by tear drainage, penetrate the cornea (passively or actively), avoid being actively effluxed back across the corneal membrane or out of the cornea or aqueous humor, avoid passive transport out of these tissues, avoid being metabolized in those tissues, and avoid being eliminated completely when the aqueous humor fluid is replenished every few hours.

25. Even after a formulation's pharmacokinetic properties are tested and understood, it is difficult (if not impossible) to ascertain which among the numerous factors affecting ocular pharmacokinetics predominate, how the factors counteract each other or otherwise interact to produce the observed result, or to what extent the various physical, chemical, or biological properties of the active compound itself impact the observed pharmacokinetic properties. Understanding the causes of a particular formulation's ocular pharmacokinetics requires an understanding of how each of the factors discussed above, which themselves are not well understood or predictable, interact in a very complicated, multifaceted system.

26. Though several of these factors, and their correlation with various physicochemical properties of the active ingredient (to the extent they are understood), are discussed below, it is important to understand that a topical ophthalmic formulation's pharmacokinetic properties are not simply a sum of the contribution of each factor, but rather the result of a complex and multi-faceted biological system artfully designed to prevent foreign compounds from penetrating into ocular tissues, and to remove those compounds that do penetrate, as quickly as possible. If a topical ophthalmic formulation's ocular pharmacokinetic

properties reliably could be predicted on the basis of simple physicochemical properties of the active compound, researchers in the field would simply design compounds that penetrate into and remain in the desired ocular tissues in high concentrations upon topical ophthalmic administration, instead of spending enormous resources testing compounds that often exhibit undesirable pharmacokinetic properties.

Precorneal Factor

27. **Tear-Protein Binding.** Upon administration of a topical ophthalmic formulation, before an active compound reaches the corneal epithelium and has a chance to be absorbed through the corneal membrane, it can bind to tear-proteins. This tear-protein binding can unpredictably alter the tear-film concentrations of the active compound.

28. The eye's lacrimal fluid contains a total protein content of approximately 0.7%, which consists of proteins such as albumin and globulin. Ex. 2 at 62-63 (Vincent H.L. Lee, "Precorneal, Corneal, and Postcorneal Factors" *in* Ophthalmic Drug Delivery Systems (Ashim K. Mitra ed. 1993)). The albumin content in the lacrimal fluid is about 0.4%. Ex. 3 at 10 (Indra K. Reddy & Madurai G. Ganesan, "Ocular Therapeutics and Drug Delivery: An Overview" *in* Ocular Therapeutics and Drug Delivery (Indra K. Reddy ed. 1996)). Moreover, protein content increases substantially in certain pathological conditions that affect the eye. Ex. 2 at 63 (Lee). The more tear-protein binding to active ingredient that occurs, the lower the tear fluid concentration of unbound active ingredient and therefore the less drug available for corneal penetration.

29. As of September 30, 1998, it was known that different fluoroquinolones bind to relevant proteins at differing levels. The literature indicated that the more lipophilic the fluoroquinolone, the more protein binding occurred. Ex. 4 at 1421 (Weiguo Liu *et al.*,

Pharmacokinetics of Sparfloxacin in the Serum and Vitreous Humor of Rabbits: Physicochemical Properties That Regulate Penetration of Quinolone Antimicrobials, Anti. Agents Chem., 42(6):1417-1423 (1998)) (showing that ciprofloxacin (least lipophilic) binds rabbit sera protein 23%, ofloxacin (moderately lipophilic) binds rabbit sera protein 33%, and sparfloxacin (more lipophilic) binds rabbit sera 42%). From this data, a person of ordinary skill in the art would have expected that the more lipophilic moxifloxacin was, the more it would bind to tear protein, thereby leaving less free moxifloxacin available for corneal penetration.

Corneal Factors

30. One factor that impacts the ocular pharmacokinetic profile of a topical formulation is passive transport. Transcellular passive transport through the corneal layers is a mechanism of ocular absorption of topical ophthalmic formulations. The rate and degree of passive transport through the corneal layers is dependent upon many factors, including but not limited to the lipophilicity, hydrophilicity, and molecular weight of the active ingredient.

31. **Lipophilicity and Hydrophilicity.** The cornea is comprised mainly of three layers: the epithelium, the stroma, and the endothelium. The corneal epithelium and endothelium are both lipophilic (fat loving), while the middle stroma layer is hydrophilic (water loving). Hence, a molecule needs to be lipophilic enough to pass through the epithelium and endothelium, and yet be hydrophilic enough to pass through the stroma.

32. As a result of this paradox, generally speaking, up to a certain point, the more lipophilic a molecule, the more it will passively transport through the cornea layers. After reaching that point, however, making a molecule more lipophilic (and hence less hydrophilic) will decrease penetration. *E.g.*, Ex. 5 at 4 (Patrick M. Hughes & Ashim K. Mitra, "Overview of Ocular Drug Delivery and Iatrogenic Ocular Cytopathologies" *in* Ophthalmic Drug Delivery

Systems (Ashim K. Mitra ed. 1993) ("Maximizing bioavailability of ophthalmic medications . . . requires the active compound be neither extremely hydrophilic or lipophilic."). The optimum value depends on each given compound or class of compounds.

33. One indicator of the relative lipophilicity/hydrophilicity of a molecule is its octanol/water partition coefficient. The octanol/water partition coefficient can be measured by suspending the molecule in question in a flask containing equal portions of buffered water (a hydrophilic medium) and octanol (a hydrophobic medium) and assessing whether (and to what extent) a compound prefers a hydrophilic or hydrophobic environment. The pH of the buffer is important, especially for compounds such as fluoroquinolones that have different charges at different pH levels. That is because the charge of a molecule often affects the partition coefficient and, more importantly, penetration across the corneal membrane. Once a molecule partitions between the octanol and water, the concentration of the molecule is measured. The result is often expressed as a log of the ratio of the concentration of the compound in octanol to the concentration of the compound in water.

34. All else equal, partition coefficients can be loosely correlated with the degree of passive transport across the cornea. As one might expect based on the principle discussed above that an optimal penetration requires a molecule that is neither too lipophilic nor too hydrophilic, many have reported a "parabolic" relationship (when graphed, the relationship takes the form of an inverted parabola or bell curve) between partition coefficient and penetration through the epithelium of the cornea. *E.g.*, Ex. 6 at 8 (Neil L. Burstein, "Basic Science of Ocular Pharmacology" *in Clinical Ocular Pharmacology* (2d ed. 1989); Ex. 5 at 4 (Hughes & Mitra);

Ex. 2 at 68 (Lee).[2] Though this relationship is generally understood, small changes in lipophilicity measured on a log scale would not be expected by a person of ordinary skill in the art to cause a significant change in corneal penetration. For example, in one of my studies, the log P values of Butyryl IDU and IsoButyryl IDU were calculated to be 0.875 and 0.840, and the corresponding corneal permeability values were found to be 5.36×10^{-6} cm/sec and 5.00×10^{-6} cm/sec, for Butyryl IDU and IsoButyrl IDU, respectively. Ex. 7 at 735 (Milind M. Narurkar & Ashim K. Mitra, *Synthesis, Physicochemical Properties and Cytotoxicity Studies of a Series of Novel 5'-Ester prodrugs of 5-Iodo-2'-Deoxyuridine*, Pharm. Research, 5(11):734-737 (1988)); Ex. 8 at 889 (Milind M. Narurkar & Ashim K. Mitra, *Prodrugs of 5-Iodo-2'-Deoxyuridine for Enhanced Ocular Transport,* Pharm. Research, 6(10):888-892 (1989)).

35. Though the inverted parabolic relationship between partition coefficient and penetration has been reported, optimal partition coefficient varies depending on the drug class and nature of the compounds studied. *See, e.g.*, Ex. 5 at 4 (Hughes & Mitra) (reporting that log of optimal partition coefficients are in the range of about 1 to 3 depending on the drug class); Ex. 2 at 11 (Reddy) (reporting that log of optimal partition coefficients are in the range of about 1 to 2 depending on the drug class)).[3]

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[2] Others have reported a sigmoidal relationship. *E.g.*, Ex. 2 at 68 (Lee, *Ophthalmic Drug Delivery*)

[3] For example, the optimal log partition coefficient for a homologous series of n-alkyl-p aminobenzoate esters was reported to be 2.5-2.6. Ex. 9 at 241-42 (G.L. Mosher & T.J. Mikkelson, *Permeability of the n-alkyl p-aminobenzoate esters across the isolated corneal membrane of the rabbit*, Int'l J. Pharm., 2:239-43 (1979)) (temperature and pH unknown). The optimal log partition coefficient for a group of 11 steroids was reported to be 2.5-3.0. Ex. 10 at 788 (Ronald D. Schoenwald & Richard W. Ward, *Relationship between Steroid Permeability across Excised Rabbit Cornea and Octanol–Water Partition Coefficients*, J. Pharm. Sci 67(6):786-788 (1978)) (measured by at 37°, pH unknown). The optimal partition coefficient for ß-blocking agents was reported to be 2.88. Ex. 11 at 1271 (Ronald D. Schoenwald and Hong-Shian Huang, *Corneal Penetration Behavior of ß-Blocking Agents I: Physiochemical Factors*, J. Pharm. Sci, 72(11):1266-1272 (1983)) (measured at 35°, pH 7.4).

36. As far as I am aware, as of September 30, 1998, there was no known optimal partition coefficient reported for the fluoroquinolone class.

37. To my knowledge, the only partition coefficient data for moxifloxacin reported as of the Alcon priority date were found in a poster presented by Bayer scientists at the ICAAC meeting in 1996. Ex. 12 (U. Peterson *et al.*, *Synthesis and In Vitro Activity of Bay 12-8039, a New 8-Methoxyquinolone* (hereinafter, "Bayer Poster"). The Bayer Poster reported that in water at 25°C, the log octanol-water partition coefficient for moxifloxacin was -1.9, and in 0.1N HCl (buffered to pH 7), the log octanol-water distribution coefficient was -0.6. The Bayer Poster did not report the partition coefficients for any other fluoroquinolone. This partition coefficient data on moxifloxacin does not itself permit an evaluation of the lipophilicity and hydrophilicity of moxifloxacin relative to other fluoroquinolones. Nor does it alone provide a basis for any meaningful assessment of the compound's ability to passively penetrate the cornea.

38. I have reviewed the literature relied upon in the expert report of Dr. Loyd Allen, as well as the other relevant literature mentioned above available as of the Alcon priority date, and I could find no study, as of September 30, 1998, which reported having measured the partition coefficient of moxifloxacin at the same time as the partition coefficients of other fluoroquinolones. However, as of the priority date, there were several studies reporting partition coefficients for other fluoroquinolones, including ofloxacin and ciprofloxacin.[4] The table below

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[4] *See, e.g.*, Ex. 13A at 93 (D.B. Jack, *Recent Advances in Pharmaceutical Chemistry. The 4-Quinolone Antibiotics*, J. Clin. Hosp. Pharm, 11:75-93 (1986)); Ex. 13B at 535-36 (Keiji Hirai *et al.*, *Differences in Susceptibility to Quinolones of Outer Membrane Mutants of Salmonella typhimurium and Escherichia coli*, 29(3):535-538 (1986)); Ex. 14 at 439-40 (John S. Chapman & Nafsika H. Georgopapadakou, *Routes of Quinolone Permeation in Escherichia coli*, Anti Agents Chem. 32(4):438-42 (1988)); Ex. 15 at 2563-65 (Noriyuki Nakanishi *et al.*, *Mechanisms of Clinical Resistance to Fluoroquinolones in Staphylococcus aureus*, Anti. Agents Chem. 35(12): 2562-67 (1991)); Ex. 16 at 381-83 (Danna L. Ross *et al.*, *Physicochemical properties of the fluoroquinolone antimicrobials. III 1-Octanol/water partition coefficients and their*

shows the reported partition coefficients (converted to a log scale) for ofloxacin and ciprofloxacin as measured in nine different studies.

REPORTED PARTITION COEFFICIENTS FOR OFLOXACIN AND CIPROFLOXACIN

	Jack pH 7.4 37°C (unknown)	Hirai pH 7.2, 25°C (aqueous phase only)	Chapman pH 7.2 unknown°C (aqueous phase only)	Nakanishi pH 7.0, unknown°C (aqueous phase only)	Ross pH 7.0, 25°C (both phases)	Takács-Novák pH 7.4 Room Temp. (aqueous phase only)	Fukuda pH 7.4, 25°C (aqueous phase only)	Montero pH 7.46 25°C (both phases)	Liu pH 7.2 25°C (both phases)
Ofloxacin	<-2.0	-0.48	-0.71	-0.60	-0.35	-0.44	-0.64	–	-0.48
Ciprofloxacin	-1.15	-1.7	-0.82	-1.22	-0.99	-1.11	-1.22	-1.13	-1.25

39. Upon reviewing this data, a person of ordinary skill could have averaged the reported partition coefficients for ofloxacin and ciprofloxacin, and compared the average reported partition coefficients for ofloxacin and ciprofloxacin to the partition coefficient for moxifloxacin reported in the Bayer Poster.[5,6] *See, e.g.*, Ex. 20 at 508-10 (Richard A. Zabinski *et*

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relationships to structure, Int'l J. Pharm., 88:379-89 (1992)); Ex. 18 at 94 (Krisztina Takács-Novák et al., *Lipophilicity of antibacterial fluoroquinolones,* Int'l J. Pharm., 79:89-96 (1992)); Ex. 17 at Tr.1, 3-4 (Masamichi Fakuda *et al.*, *Attempts to obtain basic information concerning intraocular pharmacokinetics of fluoroquinolone antibiotics through in vitro ocular experiments*, J. Oph. Soc. Jap. 99(5):532-36 (1995)) (translation); Ex. 19 at 114 (M.T. Montero *et al.*, *Influence of physicochemical properties of fluoroquinolones on encapsulation efficiency in liposomes*, Int'l J. Pharm., 138:113-20 (1996)); Ex. 4 at 1418, 1421 (Liu).

5 Before averaging, the person of ordinary skill in the art would have eliminated data points that appeared inaccurate. The log partition coefficient reported by Jack *et al.* of -2.0 is an outlier and is significantly different from each of the other seven data points for ofloxacin which all fall between -0.35 and -0.71. As a result, a person of ordinary skill in the art would not have included that data point in computing the average ofloxacin value. Indeed, Zabinksi *et al.* reported average log partition coefficients for ofloxacin of -0.47 based on fewer data points, which did not include the partition coefficient reported by Jack. Ex. 20 at 509-10 (Zabinski). Even if the ofloxacin data point from Jack *et al.* was included, however, the average partition coefficients of ofloxacin would be about -0.72, which is not appreciably different from the averages used herein.

6 Because Ross *et al.* measured both the aqueous and octanol phases when measuring the partition coefficient for each fluoroquinolone, and all of Ross *et al.*'s partition coefficient determinations were made in triplicate, if a person of ordinary skill in the art were to choose one study to compare with the partition coefficient value in the Bayer Poster to assess the relative

al., Effect of Aerobic and Anaerobic Environments on Antistaphyloccal Activities of Five Fluoroquinolones, Anti. Agents Chem., 39(2):507-12 (1995)) (reporting average partition coefficient values for fluoroquinolones measured between pH 7.0 and 7.4). If a person of ordinary skill in the art averaged the partition coefficients presented in the table above after removing outlier data, such a person would have obtained an average reported log partition coefficient for ofloxacin of -0.52 and an average reported log partition coefficient of ciprofloxacin of -1.17. If the skilled person then compared the partition coefficient of moxifloxacin reported in the Bayer Poster (-0.6) to the average partition coefficients of ofloxacin and ciprofloxacin reported in the literature, he or she would have concluded that moxifloxacin was about as, or even slightly less, lipophilic than ofloxacin, and more lipophilic than ciprofloxacin.

40. **Molecular Weight.** As noted, molecular weight of the drug can also play a role in the extent of passive transport. Generally speaking, the higher the molecular weight, the lower the penetration. Ex. 21 at 630 (Kaisa Mari Hämäläinen *et al.*, Characterization of Paracellular and Aqueous Penetration Routes in Cornea, Conjunctiva, and Sclera, Invest. Oph. & Visual Science 38(3):627-634 (1997)) (reporting that corneal permeability of PEGs decreased with increasing molecular weights)); *see also* Ex. 22 (Eric J. Lien & P.H. Wang, *Lipophilicity, Molecular Weight, and Drug Action: Reexamination of Parabolic and Bilinear Models*, J. Pharm. Sci., 69(6):648-650 (1980)) (reporting molecular weight having an impact on permeability); Ex. 23 (David S. Hull *et al.*, *Permeability of the isolated rabbit cornea to corticosteroids*, Invest. Oph. 13(6):457-58 (1974) (showing that high molecular weight molecules are impeded by epithelium).

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lipophilicity of moxifloxacin, that study would be Ross because the data in Ross appear to be most reliable.

41. The molecular weight of a compound can be calculated from a compound's empirical formula. The molecular weights of the quinolones discussed in this report are as follows in order of increasing weight: norfloxacin = 319.3 (free base); ciprofloxacin = 331.3 (free base); lomefloxacin = 351.4 (free base); ofloxacin = 361.4 (free base); levofloxacin = 361.4 (free base); and moxifloxacin = 401.4 (free base). Thus, moxifloxacin has the highest molecular weight of any of the relevant fluoroquinolones, including ofloxacin and ciprofloxacin. Thus, all things being equal (which they never actually are), one of ordinary skill in the art would expect that moxifloxacin would not be moving faster through the intact corneal epithelium relative to other fluoroquinolones.

42. In summary, passive transport (penetration across the cornea) is just one facet of ocular pharmacokinetics. But even with respect to this facet, it is clear that the multiple properties can have an impact. Indeed, at least lipophilicity can impact passive diffusion in multiple, contradictory ways. For instance, while up to a certain point, increasing lipophilicity correlates with increasing penetration across the corneal epithelium, the more lipophilic the molecule, the more tear-protein binding there may be, and hence the less passive diffusion of free compound across the corneal membrane. Lipophilicity and its affect on passive diffusion is simply one piece of the complex, and dynamic pharmacokinetic picture that is anything but clear and predictable.

Carrier Mediated Absorption

43. In addition to passive transport, drugs can be transported into the cornea and into other relevant ocular tissues with the help of membrane transporter proteins or carriers. *See, e.g.*, Ex. 24 at 73 (Claude Giasson & Joseph A. Bonanno, *Facilitated Transport of Lactate by Rabbit Corneal Endothelium*, Exp. Eye Res. 59:73-81 (1994)) (demonstrating how active transport plays

a role in transport of lactate across the cornea endothelium); Ex. 25 at 20 (Johan Stjernschantz & Maria Astin, "Anatomy and Physiology of the Eye. Physiological Aspects of Ocular Drug Delivery *in Biopharmaceutics of Ocular Drug Delivery* (Peter Edman ed. 1993)) (demonstrating the presence of a carrier mediated transport system in the ciliary epithelium); Ex. 26 at 815-818 (Richard A. Stone, *The transport of para-aminohippuric acid by the ciliary body and by the iris of the primate eye*, Invest. Oph. Vis. Sci. 18(8):807-18 (1979)) (demonstrating active transport of para-aminohippuric acid in primate iris and ciliary body). The presence of such a carrier system can dramatically impact the ocular penetration of a molecule. When a carrier system is involved in corneal transport, passive transport may be less important to overall corneal penetration.

44. As of September 30, 1998, a person of ordinary skill in the art would have understood that carrier-mediated transport was a known factor impacting the ability of a drug to be absorbed across the corneal membrane, and further would have believed that fluoroquinolones would be transported across the corneal membrane with the help of carriers. Indeed, the presence of a transporter on the cornea which can facilitate absorption of fluoroquinolones was reported by Kawazu *et al.* as early as March 1998 at the 118th Annual Meeting of the "Japan Pharmaceutical Conference" in Kyoto, Japan. *E.g.*, Ex. 27 (Goichi Kawazu *et al.*, Abstract, 118th Meeting of Pharmaceutical Society of Japan (March/April 1998) (translation).[7] An Abstract from that meeting reported that levofloxacin transport across the entire cornea exhibited concentration dependency in which the apparent permeability slowly reached a fixed value at a concentration of 25mM. In addition, it was reported that levofloxacin uptake by cultured rabbit

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[7] *See also* Ex. 28 (Kouichi Kawazu *et al.*, *Characterization of the Carrier-mediated Transport of Levofloxacin, a Fluoroquinolone Antimicrobial Agent, in Rabbit Cornea*, J. Pharm. Pharmacol., 51:797-801 (1999)); Ex. 29 (Kouichi Kawazu *et al.*, *Cultured Rabbit Corneal Epithelium Elicits Levofloxacin Absorption and Secretion*, J. Pharm. Pharmacol., 51:791-96 (1999)).

corneal epithelial cells (RCEC) reached a maximum in about 30 minutes and thereafter gradually declined. Further, in the uptake process, a concentration dependency was observed. Ex. 27 (Kawazu). Both the transport and uptake results reported by Kawazu strongly suggest the involvement of an active transport system in levofloxacin absorption through the cornea. Because fluoroquinolones were generally known to be transported across biological membranes with the help of carriers, and Kawazu reported the presence of carrier transport in the cornea, a person of ordinary skill in the art would have believed that a carrier-mediated transport mechanism would contribute to the absorption of other fluoroquinolones across the cornea. Thus, a person of ordinary skill in the art would have expected that corneal penetration of any given fluoroquinolone would likely not depend only on passive transport. Moreover, a person of ordinary skill in the art would expect that moxifloxacin, which had different chemical properties than other fluoroquinolones, would likely be actively transported into the cornea to a different degree than other fluoroquinolones but would not know whether active transport would lead to an increase or decrease in overall penetration relative to other fluoroquinolones.

Active Transport and Diffusion Out

45. **Active Transport Out.** Some molecules can be actively removed, such as by organic anionic transporters or efflux pumps, from inside a membrane to outside a membrane. Thus, even if a drug penetrates well into a membrane, if it is effluxed, the penetration is effectively counteracted and becomes far less physiologically relevant.

46. It has been known for decades that some drugs are actively transported out of eye tissues, which causes diminished concentrations in those tissues. *See, e.g.*, Ex. 30 at 723 (Michael Barza *et al.*, *The effects of infection and probenecid on the transport of carbenicillin from the rabbit vitreous humor*, Invest. Oph. Vis. Science 22:(6):720-26 (1982)) (explaining that

B-lactam antibiotics are actively transported out of rabbit eyes via a pump in retina); Ex. 31 at 1605 (Michael Barza *et al.*, *Pharmacokinetics of Intravitreal Carbenicillin, Cefazolin, and Gentamicin in Rhesus Monkeys*, Invest. Oph. Vis. Science 24(12):1602-06 (1983)) (explaining that B-lactam antibiotics are actively transported out of monkey eyes via a pump in retina); Ex. 32 at 461 (Bernard Becker & Max Forbes, *Iodopyracet (Diodrast) transport by the rabbit eye*, Am. J. Physio. 200(3):461-64 (1961)) (reporting active transport of iodopyracet out of the eye); Ex. 33A at 485 (J.G. Cunha-Vaz & D.M. Maurice, *The active transport of fluorescein by the retinal vessels and the retina*, J. Physiol. 191:467-86 (1967)) (reporting the active transport of fluoroscein out of the retina).

47. Drugs that are substrates for active transport systems are actively transported out of ocular tissues to different degrees, which can have a dramatic effect on drug half-life relative to other drugs in the same class. Ex. 31 at 1605 (Barza, *Rhesus Monkeys*). For example, the half-life of the B-lactam antiobiotic, Carbenicillin, in rhesus monkeys increased from 10 to 20 hours in the vitreous humor, and from 8 hours to 39 hours in the aqueous humor, upon administration of probenecid, which blocks the action of an active transporter. *Id.* In addition, the half-life of the B-lactam antiobiotic, Cefazolin, in rhesus monkeys increased from 7 hours to 30 hours in the vitreous humor, and from 7 hours to 31 hours in the aqueous humor, upon administration of probenecid. *Id.*

48. As of September 30, 1998, it was known that different fluoroquinolones were being actively transported out of various ocular tissues at different rates. For example, Liu *et al.* reported that fluoroquinolones were being actively transported out of the vitreous, and that this efflux occurred at different rates depending on the fluoroquinolone and whether the tissue was inflamed. Ex. 4 at 1417, 1420-22 (Liu) ("We have shown that quinolones, like beta-lactam

antiobiotics, are exported from the vitreous humor via a pump which is blocked by probenecid and inflammation."). Furthermore, Liu *et al.* reported that probenecid significantly increased the half-lives of ciprofloxacin, fleroxacin, and sparfloxacin, but not ofloxacin. *Id.* at 1420-22. This indicates that ofloxacin was not as susceptible to active transport out of the vitreous as the other fluoroquinolones. *Id.* Thus, Liu demonstrated that the extent to which a fluoroquinolone is actively effluxed is not simply a function of its lipophilicity.

49. One of ordinary skill in the art would have expected that this same type of active transport mechanism was present in the aqueous humor. As early as 1979, Reddy *et al.* reported the existence of the same active transport mechanisms in both the vitreous and aqueous humor. Ex. 33B (Venkat N. Reddy, *Dynamics of transport systems in the eye*, Invest. Oph. Vis. Sci.; 18(10):1000-18 (1979)).

50. Furthermore, Saha *et al.* had reported the existence of a p-Glycoprotein drug efflux pump in the conjuctiva which works to restrict the overall absorption of drugs. Ex. 34A at 1221 (Pratik Saha *et. al.*, *Existence of a p-Glycoprotein Drug Efflux Pump in Cultured Rabbit Conjuctival Epithelial Cells*, Invest. Oph. Vis. Sci. 39(7):1221-26 (1998)). Because it was known to a person of ordinary skill in the art as of the priority date that the cornea is an extension of the conjunctiva and the two tissues are connected, a person of ordinary skill in the art would have expected that a p-Glycoprotein drug efflux pump existed in the cornea, which would restrict the overall absorption of drugs into the cornea.[8]

51. Based on the available literature, a person of ordinary skill in the art would have expected that active transporters would likely play an important role in the ocular

[8] This has since been proven by Kawazu *et al.* Ex. 34B (Kouichi Kawazu *et al.*, *Characterization of Cyclosporin A Transport in Cultured Rabbit Corneal Epithelial Cells: P-Glycoprotein Transport Activity and Binding to Cyclophilin*, Invest. Oph. and Visual Science, 40(8):1738-1744 (1999)).

pharmacokinetics of fluoroquinolones, but would not have known or reasonably expected how this factor would impact moxifloxacin relative to other fluoroquinolones.

52. **Diffusion Out.** In addition to active efflux out of the ocular tissues, active compounds are also known to passively diffuse from those tissues. Like active transport out, passive diffusion out of tissues also can have a dramatic effect on the maximum concentration and half-life of a compound in the relevant ocular tissues.

53. Liu *et al.* reported that the more lipophilic a molecule, the shorter its half-life in the vitreous humor. Ex. 4 at 4120 (Liu). Thus, sparfloxacin, one of the more lipophilic fluoroquinolones, has a shorter half-life in the vitreous than ciprofloxacin, ofloxacin, and fleroxacin. *Id.*

54. The principle that passive transport out of ocular tissues depends, in part, on the lipophilicity of the molecule applies with equal force to passive transport out of the aqueous humor and the iris-ciliary body. Thus, for instance, others reported before the priority date of the '830 patent that the more lipophilic the molecule, the shorter the elimination half life in the aqueous and iris-ciliary body. *E.g.*, Ex. 35 (Thomas F. Freddo *et al.*, *The source of Proteins in the Aqueous Humor of the Normal Rabbit*, Invest Oph. Vis Sci. 31(1):125-37 (1990)).

55. From these reports, a person of ordinary skill in the art would have expected that if moxifloxacin were more lipophilic relative to other fluoroquinolones, it would have a shorter elimination half life in the various tissues of the eye. This is significant because a compound needs to stay in a tissue long enough to kill the bacteria present there. Hence, even if a person of ordinary skill in the art believed that lipophilicity would lead to higher penetration, he or she would be equally concerned that the same physiochemical characteristic would cause shorter half lives in the relevant ocular tissues.

56. **Melanin Binding.** The iris and ciliary bodies are known to have melanin that binds to drugs and helps retain the drugs in those tissues. Because of this binding, the iris-ciliary body serves as a depot for a compound which helps to replenish the loss of drug through aqueous humor turnover, thereby extending the residence time in ocular tissues. Ex. 25 at 19-20 (Edman) (explaining that many drugs with amine groups and that are cations bind melanin in the iris, and that drug melanin complex forms a slow release system)); Ex. 6 at 10 (Burnstein) ("[T]he iris can serve as a depot or reservoir for some drugs, concentrating and then releasing them for longer than otherwise expected."); *see also* Ex. 36 at 209 (Patrick M. Hughes *et al.*, *Vitreous disposition of Two Acycloguanosine Antivirals in the Albino and Pigmented Rabbit Models: A Novel Ocular Microdialysis Technique*, J. Ocul. Pharm. Ther. 12(2):209-24 (1996)). The extent of melanin binding is thought to be dependent on the lipophilicity of the molecule. Ex. 6 at 10 (Burnstein). Because a person of ordinary skill in the art would have reasonably expected that the partition coefficient for moxifloxacin was similar to ofloxacin, he or she would have also expected to exhibit similar binding properties to melanin as ofloxacin.

C. Ocular Pharmacokinetics of the Claimed Moxifloxacin Formulation

57. The penetration rate into and concentration achieved in the ocular tissues is very high and unexpectedly far superior to ofloxacin and ciprofloxacin when applied in the formulation recited in claim of the '830 patent.

58. In one study, a 0.5% moxifloxacin topical ophthalmic formulation was compared to a 0.3% ofloxacin topical ophthalmic formulation and maximal concentrations were measured in the aqueous humor, cornea, and vitreous. In the aqueous humor, maximal concentrations were 1.42 μg/ml for moxifloxacin and 0.405 μg/ml for ofloxacin, which is more than a three-fold difference. In the cornea, maximal concentrations were 24.8 μg/g for moxifloxacin and 8.01 μg/g for ofloxacin, which is about a three-fold difference. And in the vitreous, the maximal

concentrations for moxifloxacin were 0.082 μg/g and 0.003 μg/g for ofloxacin, which is about a twenty-five fold difference. Ex. 37 (Robertson *et al.*, ARVO Abstract 4906 (2004)).

59. If one of ordinary skill in the art were to have estimated the lipophilicity of moxifloxacin relative to ofloxacin and ciprofloxacin based on the average partition coefficient values available in the prior art, and then estimated penetration based solely on partition coefficient (which, as explained above, would have been improper because it ignores other factors, *e.g.*,active transport), such a person would have estimated that moxifloxacin would reach about the same concentration as ofloxacin if applied in the same amounts topically to the eye. Taking into account the difference in the amount of moxifloxacin (0.5%) used in the study above relative to ofloxacin (0.3%), one of ordinary skill would have estimated that moxifloxacin would achieve less than a two-fold higher maximum concentration in these tissues. But as shown by this data, moxifloxacin's maximum concentration is in fact three to four times higher in the cornea and aqueous humor, and twenty-five times higher in the vitreous humor, which is entirely unexpected.

60. Furthermore, Fukada *et al.* reported a penetration rate (permeability coefficient) for ofloxacin about 2.75 times higher than that of ciprofloxacin. Ex. 17 at 1-2 (Fakuda). Based solely on a comparison between the partition coefficient in the Bayer Poster and the average partition coefficient reported in the literature (which, again, would be ignoring other factors), one of ordinary skill would have estimated that moxifloxacin would have the same penetration rate as ofloxacin, and thus penetrate about 2.75 times better than ciprofloxacin.

61. But this is not the case. In an Alcon study comparing the *ex vivo* corneal penetration of fluoroquinolones under steady state conditions, as shown by the graph and table attached as Ex. 38 (the table from which is reproduced below), moxifloxacin's penetration rate in

cm/s, *i.e.*, its permeability coefficient, is far superior to both ofloxacin and ciprofloxacin (and much more superior to ciprofloxacin than ofloxacin is).

Ex Vivo Corneal Penetration Apparent Permeability Coefficients & Lag Time of Fluoroquinolones		
Fluoroquinolone	**Permeability Coefficient ($\times 10^{-7}$ cm/sec)**	**Lag Time (min)**
Ofloxacin	50 ± 10	66 ± 3
Ciprofloxacin	18 ± 2	70 ± 12
Norfloxacin	22 ± 2	71 ± 6
Moxifloxacin	91 ± 9	49 ± 1
Levofloxacin	29 ± 8	69 ± 13
Gatifloxacin	25 ± 2	99 ± 12
Lomefloxacin	35 ± 2	78 ± 1

62. Indeed, this study found that moxifloxacin's permeability coefficient was nearly 2 times that of ofloxacin's permeability coefficient and five times that of ciprofloxacin's permeability coefficient, which are unexpected results. Ex. 38 (steady state table). This study further illustrated that at steady state, moxifloxacin concentrations in the cornea continued to increase at a much faster (µg/min) rate than any of the other fluoroquinolones tested, and reached a total concentration of over two times higher than ofloxacin after 300 minutes, and seven times higher than ciprofloxacin after 300 minutes. *Id.* (steady state graph).

63. In a separate head-to-head study between topical ophthalmic formulations of 0.5% moxifloxacin and 0.3% ciprofloxacin, Salomon *et al.* illustrated that the mean aqueous concentration of moxifloxacin was 1.31 µg/ml, which is more than 8-times higher that the mean aqueous concentrations of ciprofloxacin, which was 0.15 µg/ml. Ex. 39 at 468 (Renée Solomon, *Penetration of Topically Applied Gatifloxacin 0.3%, Moxifloxacin 0.5%, and Ciprofloxacin 0.3% into the Aqueous Humor*, Oph., 112(3):466-69 (2005)). Based only on the concentration

difference of the two formulations in the Solomon study, one skilled in the art would expect moxifloxacin's ocular tissue concentrations to be about two times (5/3) higher than that of ciprofloxacin. On the basis of the information available as of September 1998, a person of ordinary skill in the art would not have expected an 8-fold difference in the mean aqueous concentration of ciprofloxacin and moxifloxacin.

64. This superior ocular pharmacokinetic data discussed in ¶¶ 59-64 could not have been expected on the basis of the information available in September 1998, and is not even explicable on the basis of hindsight. By way of example, the relative partition coefficients for ofloxacin and moxifloxacin gleaned from the Bayer Poster and the average reported value in the prior art simply do not explain these results.

65. These data are also surprising given that moxifloxacin accumulates to a much greater degree than ofloxacin and other relevant fluoroquinolones in the conjunctiva, which means that there should be less moxifloxacin available to penetrate through the cornea and enter the relevant tissues via the corneal route. *See* Ex. 40 (Rudolph S. Wagner *et al.*, *Evaluation of Moxfloxacin, Ciprofloxacin, Gatifloxacin, Ofloxacin, and Levofloxacin Concentration in Human Conjuctival Tissue*, Arch. Oph., 123:1182-83 (2005)).

66. Finally, the superior penetration of moxifloxacin is present across the entire range of moxifloxacin concentrations (0.1% to 1.0%) recited in claim 1 of the '830 patent. Data obtained using the penetration model reported by Schoenwald *et al.* shows that there is an approximately linear increase in flux (the rate at which the compound crosses the membrane) and accumulation as the concentration of moxifloxacin increases. See Ex. 41 (Corneal Perfusion Table and Graph); Ex. 11 (Schoenwald and Huang). Based on these results, the superior

pharmacokinetic properties of the moxifloxacin formulation that I have discussed in this report are present across this 0.1% to 1.0% range of concentrations.

September 19, 2007

Ashim K. Mitra

Ashim K. Mitra, Ph.D

EXHIBIT B

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December 7, 2007

VIA ELECTRONIC MAIL

Douglas A. Robinson, Esq.
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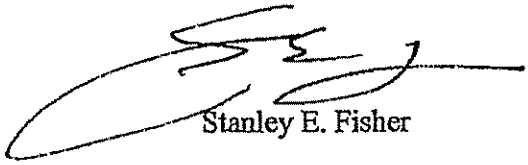
Re: Bayer HealthCare AG et al. v. Teva Pharmaceuticals USA, Inc., No 06-234 (SLR)

Dear Doug:

During the deposition of Dr. Ashim K. Mitra on November 6, 2007, you asked Dr. Mitra questions relating to the protocol employed by Alcon in reaching the results illustrated in Exhibits 38 and 41 to Dr. Mitra's report. On November 20, 2007, in response to the questions posed by you at Dr. Mitra's deposition, Alcon produced documents Bates numbered AL010-001000-1065, AL010-002000-2025, and AL0010-003000-3059. This letter is to inform you that Dr. Mitra intends to rely on these documents at trial to the extent necessary.

Please contact me if you would like to discuss these matters further.

Sincerely,



Stanley E. Fisher

EXHIBIT C

Exhibit C

E-Mail Request for Emergency Relief

1. Case Number: 06-cv-234-SLR

2. Check the box that applies:

☑ Requesting a teleconference with the parties and the court
☐ Requesting an in-person conference with the parties and the court
☐ Requesting either of the above listed options at the court's determination

3. BRIEFLY describe the reason for this **emergency** request:

I write for defendant Teva. Although the Court's Feb. 13 order allowed the parties until March 10 to submit deposition testimony to the court reporter (and the parties did that), Teva requests the opportunity to submit short additional portions to rebut testimony given on the last day of trial, such as Dr. Zhanel's recounting of Bayer's research activities, which he stated he gleaned through conversations he had with Bayer personnel, but which were not disclosed in his Rule 26 report or otherwise prior to trial. We did not receive the transcript of the last trial day until late on March 7, while counsel were traveling. Once we had reviewed the last day's testimony, we provided Alcon with proposed additional designations on March 11 and 12. Alcon has not agreed to these submissions, even though Teva has agreed that Alcon can counter-designate. Teva requests a brief teleconference to explain its request.

*Any text added beyond the limits of this space will be disregarded by the court.

4. Name of opposing counsel contacted about this request: Frederick L. Cottrell, III

5. Response of opposing counsel to this request:

Counsel for Teva and Alcon exchanged many letters this week. I know that Alcon opposes Teva's additional designations. I do not know yet whether Alcon opposes a teleconference.

6. Name of local counsel making this request: Richard D. Kirk (rk0922)

7. Today's Date: March 14, 2008

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For court use only:

☐ A teleconference will be held on _____ to be coordinated and initiated by

☐ An in-person discovery conference will be held on:

☑ Other: Teva's Request is denied.

Opposing Counsel's Response to E-Mail Request for Emergency Relief

1. Case Number: 06 -cv- 234 -SLR

2. BRIEFLY state your response to the **emergency** request made by opposing counsel:

Alcon objects to Teva's untimely and prejudicial submission of deposition testimony from Drs. Bremm and Petersen. Teva first raised these designations after both the trial and the March 10 deadline for submitting deposition testimony. More importantly, both witnesses were available to testify at trial if Teva wanted testimony from them, making Teva's attempted use of their depositions inappropriate. Alcon's inability to elicit testimony from these witnesses to place in context the deposition testimony is highly prejudicial. Teva's reliance on Dr. Zhanel's testimony to excuse its untimely submission is misplaced, as it was Teva that first elicited testimony regarding the topic at issue during cross-examination. Alcon requests an in-court conference to demonstrate that Teva's attempt to reopen the trial to present additional evidence is contrary to the Federal Rules and highly prejudicial.

*Any text added to beyond the limits of this space will be disregarded by the court.

3. Name of local counsel submitting this response: Frederick L. Cottrell, III

4. Today's Date: March 17, 2008

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